

# ABNORMAL CENTRAL VENOUS OXYGEN SATURATION AS A PREDICTOR OF MORTALITY IN PATIENTS WITH SEPSIS AND POLYTRAUMA IN THE SURGICAL INTENSIVE CARE UNIT.

A prospective observational study to characterise the association of abnormal central venous oxygenation and mortality in patients with sepsis and polytrauma.

**Dissertation submitted in partial fulfillment  
of the requirement of The Tamil Nadu Dr.  
M.G.R. Medical University for the M.D.  
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be held in September 2012.**

## ***CERTIFICATE***

**This is to certify that “ *Abnormal central venous oxygen saturation as a predictor of mortality in patients with sepsis and polytrauma in the surgical intensive care unit* ” is a bonafide work of Dr. Jyothi Avula in partial fulfilment of the requirements for the M.D. Anaesthesiology examination (Branch X) of The Tamil Nadu Dr. M.G.R Medical University to be held in September 2012.**

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# AIMS AND OBJECTIVES

## AIM

To test the hypothesis that abnormal central venous oxygen saturation (ScvO<sub>2</sub>) is associated with high mortality in patients with sepsis and polytrauma.

## OBJECTIVES

- 1) To assess the effect of abnormal (low and supranormal) central venous oxygen saturation (ScvO<sub>2</sub>) and incidence of morbidity and mortality in the population who are admitted with the diagnosis of sepsis and polytrauma to our surgical ICU.
- 2) To explore the relationship between abnormal (low and supranormal) central venous oxygen saturation (ScvO<sub>2</sub>) and lactates with outcome of SICU admission among sepsis and polytrauma patients.
- 3) To estimate the correlation between central venous oxygen saturation (ScvO<sub>2</sub>) and the following
  - APACHE II score
  - Duration of ICU stay
  - Length of ventilated days and inotropic support
  - Coagulopathy and dialysis requirement

# ABSTRACT

**TITLE :** A prospective observational study to characterize the association of abnormal central venous oxygen saturation to the morbidity and mortality in patients admitted to the surgical intensive Care unit with a diagnosis of sepsis or polytrauma.

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**OBJECTIVES -** Abnormal (low and supranormal) central venous oxygen saturation (ScvO<sub>2</sub>) with associated hyperlactatemia has been shown to be associated with increased mortality in post-operative cardiac surgery patients and in patients with sepsis. We want to assess the effect of these and incidence of morbidity and mortality in the population who are admitted with a diagnosis of sepsis and poly trauma to our surgical ICU.

**METHODS** – A prospective observational study was done in all patients who met the inclusion criteria and had a diagnosis of sepsis and polytrauma. They were assessed during initial 6 hours and their SCV02 was measured at admission and 6 hours later and its association to mortality and other variables like lactates and base excess and duration of icu stay and inotropic support were assessed and analysed using a multivariate model analysis.

**RESULTS** - When compared to the normal group, the hyperoxia group had a risk ratio of 2.422 times more likelihood of mortality and the hypoxia group had 1.0256 times more likelihood of mortality. When the hypoxia group was compared with the hyperoxia group the risk ratio for mortality was 2.36 times more in the hyperoxia group though the p value was not significant.

There was no statistically significant difference between the 3 groups of Scv02 when compared to duration of icu stay, duration of inotropic support and coagulopathy and need for dialysis and apache11 score and base excess and lactates.

**CONCLUSIONS** – When lactates, base excess and Scv02 were compared to mortality though not significant; gave a j shaped curve suggesting that mortality is higher both in the hypoxia and the hyperoxia group compared to the normoxia group. The small sample size though was adequate to predict a trend, was insufficient to address secondary objectives.



# INTRODUCTION

Sepsis and trauma are major causes of mortality and morbidity in ICU patients. The common feature in these two conditions is systemic inflammation and deranged oxygen delivery. Unfortunately, until recently, numerous therapies to treat sepsis failed to improve mortality. The three main resuscitation targets are preload (measured by central venous pressure), perfusion (mean arterial pressure), and tissue hypoxia (base excess and blood lactate). The Early Goal Directed therapy (EGDT) trial in septic patients whose haemodynamic parameters were optimized within the first 6 hours after hospital admission showed an improved outcome. The trial demonstrated that optimization oxygen delivery by optimizing central venous oxygen saturation and mean arterial blood pressure improved outcome. Central venous oxygen saturation is obtained by measuring the oxygen saturation in venous blood returning to the heart. In simple form, it represents the balance between oxygen delivery and oxygen consumption which is an indication of oxygen extraction. In sepsis and trauma, oxygenation of blood in the lungs, delivery of oxygenated blood to the tissues, and utilization of oxygen by various tissues are affected by various mechanisms. Early Identification and treatment of this imbalance in oxygen delivery and utilization will prevent organ failure and reduce morbidity and mortality in the ICU patients.(1)

Thus, a low ScvO<sub>2</sub> may indicate a decrease in systemic oxygen delivery, an increase in oxygen extraction or a combination of the two. In the EGDT protocol, a low ScvO<sub>2</sub> is addressed through oxygen delivery optimization by improving arterial oxygen saturation, cardiac output, or oxygen carrying capacity to increase oxygen delivery. Accordingly, one may broadly categorize deficiencies in oxygen exchange into three types of failure: 1) macro circulatory failure, 2) microcirculatory failure, and 3) mitochondrial failure. Macro

circulatory failure is typically assessed through parameters such as central venous pressure (CVP), mean arterial pressure (MAP) and cardiac output. A reduction in any of these parameters can result in an inadequacy in the net amount of oxygen delivered to the tissues. The cause of microcirculatory failure is multi factorial and includes physiologic shunting, maldistributed flow, increased micro vascular permeability, and micro vascular thrombosis. In some instances, there may be adequate macro circulatory flow but microcirculatory failure prevents the oxygen from reaching tissues. Finally, in mitochondrial failure, oxygen is presented to the cell but the mitochondria are dysfunctional and unable to process the oxygen. In the latter two cases, the ScvO<sub>2</sub> may actually be elevated-a condition referred to as tissue dysoxia.(2)

The clinical impacts of abnormally low and high ScvO<sub>2</sub> values in patients who receive the same protocol are not well characterized. The notion of abnormally elevated ScvO<sub>2</sub> levels representing hypoxia at the cellular level has been reported but there is little evidence in support of its clinical significance. Furthermore, since the EGDT-based protocol aims to correct a low ScvO<sub>2</sub> level through a titrated resuscitation, it is not clear whether the initial ScvO<sub>2</sub> level and/or the maximum ScvO<sub>2</sub> achieved have an association with mortality. In a study done both low (60.8%) and supranormal (77.4%) ScvO<sub>2</sub> were associated with an unfavourable course.

Patients with low ScvO<sub>2</sub> and an uneventful course initially presented with normal lactate levels, whereas patients with supra normal ScvO<sub>2</sub> displayed consistently higher serum lactate levels. High ScvO<sub>2</sub> values were associated with the signs of systemic inflammation. Mortality rates in the patient groups presenting either low (14.8%) or supra normal ScvO<sub>2</sub> (7.9%) and higher than normal (0%). This was significant ( $p < 0.001$ ). Blood

Lactate was increased in patients who ultimately died, irrespective whether they had low or supra normal ScvO<sub>2</sub> values. High ScvO<sub>2</sub> is an under-recognized warning sign for impaired tissue oxygenation in patients with sepsis.

Supra normal values of ScvO<sub>2</sub>, which are traditionally considered to be of limited clinical value, turned out to be under-recognized warning signs of impaired tissue oxygenation in cardiac surgery patients. The study group have proposed that combined analysis of ScvO<sub>2</sub> and lactate levels may be used to identify patients at risk, and a high ScvO<sub>2</sub> might reflect an under recognized warning sign. In this context, additional studies are warranted to test these results in other groups of acutely ill patients.(3)

ScVO<sub>2</sub> monitoring can be an early indicator of bleeding, estimated blood loss, and may affect the decision to transfuse. In a study of 26 trauma patients, Scalea and colleagues found that the 10 patients who had ScVO<sub>2</sub> less than 65% had more serious injuries, significantly larger estimated blood losses, and required more transfusions than those patients with ScVO<sub>2</sub> greater than 65%. In this study linear regression coefficients showed that ScVO<sub>2</sub> was better than heart rate, MAP, CVP, pulse pressure, and urine output in predicting estimated blood loss.

Global tissue hypoxia is one of the most important factors in the development of MODS. In hemodynamically unstable critically ill patients, superior venacaval oxygen saturation (ScVO<sub>2</sub>) and mixed venous saturation (SVO<sub>2</sub>) monitoring has been shown to be a better indicator of global tissue hypoxia than vital signs and other clinical parameters alone. ScVO<sub>2</sub> monitoring can have diagnostic and therapeutic uses in understanding the efficacy of interventions in treating critically ill, hemodynamically unstable patients.(4)

In this prospective observational study, we aimed to characterize the association of abnormal (low and supranormal) central venous oxygen saturation (ScvO<sub>2</sub>) to the course and mortality

in patients admitted to surgical intensive care unit with a diagnosis of sepsis and trauma. Our aim is to test the hypothesis that abnormal ScvO<sub>2</sub> is associated with high mortality in patients with sepsis and polytrauma.(5)(6)

# LITERATURE REVIEW

## INTRODUCTION TO SEPSIS

Sepsis and septic shock are as common and lethal as any other acute lethal conditions that any physician routinely confront such as myocardial infarction, stroke and trauma.

The story of sepsis over the past 100 years has been a fascinating tale of discovery. Great strides have been made in terms of understanding the extra and intracellular events that contribute to organ system dysfunction. There has also been progress in management, with several studies suggesting reduced mortality rates as a result of improved supportive and pharmacologic management of these critically ill patients. Widely publicized evidence-based guidelines have been published to help the clinician manage the patient with severe sepsis. However, mortality rates still remain unacceptably high (30-50%) and it is apparent that much remains to be done to advance our understanding and treatment of this common condition.(7)

The systemic inflammatory syndrome can be self-limited or can progress to severe sepsis and septic shock. These are conditions with mortality rates approaching up to fifty percent. The normal host response to infection is a complex process that localises and controls invasion and initiates repair of injured tissues, a process during which there is activation of several inflammatory mediators. Severe sepsis results when the host response to infection becomes generalised involving tissues remote from site of injury.(8)

## DEFINITIONS

Sepsis is defined as the presence or presumed presence of an infection accompanied by evidence of a systemic response called the systemic inflammatory response syndrome (SIRS).(9)

Systemic inflammatory response syndrome is defined as the presence of 2 or more of the following:

- (1) Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F);
- (2) Pulse rate greater than 90 beats/min.
- (3) Respiratory rate greater than 20 breaths/min (or PaCO<sub>2</sub> less than 32 mm Hg)
- (4) WBC count greater than 12,000/mm<sup>3</sup> or less than 4,000/mm<sup>3</sup>, or greater than 10% immature cells (band forms).(8)

The new definition, although more comprehensive than systemic inflammatory response syndrome, is vague in its requirement of some of the many clinical and laboratory findings in addition to suspicion of infection. By definition, sepsis describes only the presumed existence of an infection and at least a minimal systemic response and therefore would not necessarily imply the existence of hemodynamic compromise or a bacterial cause, as is often suggested.

Septic shock can be viewed as severe sepsis with cardiovascular failure (organ perfusion).

**Definitions of systemic inflammatory response syndrome (SIRS) and different degrees of severity of sepsis(8)**

Condition	Description
<b>Systemic inflammatory response syndrome</b>	Two or more of the following conditions: temperature $>38.5^{\circ}\text{C}$ or $<35.0^{\circ}\text{C}$ ; heart rate of $>90$ beats/min; respiratory rate of $>20$ breaths/min or $\text{PaCO}_2$ of $<32$ mm Hg; and WBC count of $>12,000$ cells/mL, $<4000$ cells/mL, or $>10$ percent immature (band) forms
<b>Sepsis</b>	SIRS in response to documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection, e.g., ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
<b>Severe sepsis</b>	Sepsis and at least one of the following signs of organ hypoperfusion or organ dysfunction: areas of mottled skin; capillary refilling of $\geq 3$ s; urinary output of $<0.5$ mL/kg for at least 1 h or renal replacement therapy; lactate $>2$ mmol/L; abrupt change in mental status or abnormal

	<p>EEG findings; platelet count of &lt;100,000 cells/mL or disseminated intravascular coagulation; acute lung injury or ARDS; and cardiac dysfunction (echocardiography)</p>
<b>Septic shock</b>	<p>Severe sepsis and one of the following conditions: systemic mean BP of &lt;60 mm Hg (&lt;80 mm Hg if previous hypertension) after 20 to 30 mL/kg starch or 40 to 60 mL/kg saline solution, or PCWP between 12 and 20 mm Hg; and need for dopamine of &gt;5 mcg/kg/min, or norepinephrine or epinephrine of &lt;0.25 mcg/kg/min to maintain mean BP at &gt;60 mm Hg (80 mm Hg if previous hypertension)</p>
<b>Refractory septic shock</b>	<p>Need for dopamine at &gt;15 mcg/kg/min, or norepinephrine or epinephrine at &gt;0.25 mcg/kg/min to maintain mean BP at &gt;60 mm Hg (80 mm Hg if previous hypertension)</p>



## **EPIDEMIOLOGY**

Approximate incidence of severe sepsis from existing data is three per thousand persons per year, and of those 50% - 70% need intensive care treatment with an overall hospital mortality of 30% - 50%. The incidence increases exponentially with age suggesting the number of cases will increase in coming years as the population grows older.(7)(8)

Till 2003 it was the same ICD (international classification of diseases) code for all definitions of sepsis. Now severe sepsis and septic shock have separate code under the ICD 9. This was proposed to distinguish high-risk patients from patients with sepsis.(8)

Recent estimates indicate that the rate of severe sepsis hospitalizations doubled during the last decade and that age-adjusted population-based mortality is increasing.

## **PATHOPHYSIOLOGY**

A series of pathogenic events are responsible for the transition from sepsis to severe sepsis or septic shock. The initial reaction to infection is a neurohumoral, generalized pro- and anti-inflammatory response. This begins with a cellular activation of monocytes, macrophages, and neutrophils that interact with endothelial cells through numerous pathogen recognition receptors. A further host response includes the mobilization of plasma factors as a result of this cellular activation and endothelial disruption. These plasma factors include cytokines such as tumour necrosis factor, interleukins, caspase, proteases, leukotriene's, kinins, reactive oxygen species, nitric oxide, arachidonic acid, platelet activating factor, and eicosanoids.

Activation of the complement and coagulation cascades further amplifies this elaborate chain of events. The vascular endothelium is the predominant site of these interactions, and, as a result, there is microvascular injury, thrombosis, and a loss of endothelial integrity (capillary leak), resulting in tissue ischemia. This diffuse endothelial disruption is responsible for the various organ dysfunctions and global tissue hypoxia that accompany severe sepsis or septic shock. Key therapies that have led to mortality benefits in severe sepsis or septic shock are directed at reversing these pathogenic mechanisms.(8)

## STEPS IN PATHOPHYSIOLOGY OF SEPSIS

### Normal response of host to infection

Initially there is binding of immune cell surface receptors like pattern recognition receptors (PRRS) and triggering receptors expressed on myeloid cells (TREM-1) and myeloid –DAP12-associating lectin (MDL1) to the microbial components. This has multiple effects including activation of host inflammatory response, the pro-inflammatory mediators (TNF A and IL1) which leads to recruitment of more polymorphonuclear leucocytes (PMN's) and macrophages and anti-inflammatory mediators (CYTOKINES). If these mediators balance each other and the initial infectious insult is overcome, homeostasis will be restored, the end result being tissue repair and healing.(8)

## Transition to sepsis

Sepsis occurs when the release of proinflammatory mediators in response to either infectious or non-infectious conditions exceeds the boundaries of local environment leading to a more generalised response. Sepsis can be conceptualised as a malignant intravascular inflammation as it is uncontrolled, unregulated, self-sustained and spreads via blood and is an exaggeration of normal inflammatory response.

The cause is likely multifactorial and may include :

- Direct effects of endotoxins released by the micro-organisms
- Excess pro-inflammatory mediators
- Complement activation
- Genetic susceptibility (SNP-single nucleotide polymorphs)

## *Systemic effects of sepsis*

Widespread cellular injury may occur when the immune response becomes generalized. Cellular injury is the precursor to organ dysfunction. The precise mechanism of cellular injury is not understood, but its occurrence is indisputable as autopsy studies have shown widespread endothelial and parenchymal cell injury.

*Mechanisms proposed to explain the cellular injury include:*

Tissue ischemia (insufficient oxygen relative to oxygen need), cytopathic injury (direct cell injury by proinflammatory mediators and or other products of inflammation), and an altered rate of apoptosis (programmed cell death).

Tissue hypoperfusion can be present even in the presence of normal blood pressure and adequate cardiac output, a state sometimes called as cryptic shock. This may be due to preferential maldistribution of blood flow at the microvascular level or related to mitochondrial dysfunction in the presence of adequate substrate delivery.

### *Tissue ischaemia*

Significant derangement in metabolic autoregulation, the process that matches oxygen availability to changing tissue oxygen needs, is typical of sepsis. Microcirculatory lesions may be the result of imbalances in the coagulation and fibrinolytic systems, both of which are activated during sepsis.

Endothelial lesions may be a consequence of interactions between endothelial cells and activated polymorphonuclear leukocytes (PMNs). The increase in receptor-mediated neutrophil-endothelial cell adherence induces the secretion of reactive oxygen species, lytic enzymes, and vasoactive substances (nitric oxide, endothelin, platelet-derived growth factor, and platelet activating factor) into the extracellular milieu, which may injure the endothelial cells.

### *Cytopathic injury*

Proinflammatory mediators and other products of inflammation may cause sepsis-induced mitochondrial dysfunction (e.g., impaired mitochondrial electron transport) via a variety of mechanisms, including direct inhibition of respiratory enzyme complexes, oxidative stress damage, and mitochondrial DNA breakdown . Such mitochondrial injury leads to cytotoxicity.(10)

The clinical relevance of mitochondrial dysfunction in septic shock was suggested by a study of 28 critically ill septic patients who underwent skeletal muscle biopsy within 24 hours of admission to the ICU . Skeletal muscle ATP concentrations, a marker of mitochondrial oxidative phosphorylation, were significantly lower in the 12 patients who died of sepsis than in 16 survivors. In addition, there was an association between nitric oxide overproduction, antioxidant depletion, and severity of clinical outcome. Thus, cell injury and death in sepsis may be explained by cytopathic (or histotoxic) anoxia, which is an inability to utilize oxygen even when present.(10)

### *Apoptosis*

During sepsis, proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils, thereby prolonging or augmenting the inflammatory response and contributing to the development of multiple organ failure. Sepsis also induces extensive lymphocyte and dendritic cell apoptosis, which alters the immune response efficacy and results in decreased clearance of invading microorganisms. Apoptosis of lymphocytes has been observed at autopsies in both animal and human sepsis. The extent of lymphocyte apoptosis correlates

with and the severity of the septic syndrome and the level of immunosuppression. Apoptosis has been also observed in parenchymal cells, endothelial, and epithelial cells. Several experimental studies show that inhibiting apoptosis protects from organ dysfunction and lethality.(8)

### *Organ specific effects of sepsis*

No organ system is spared from the consequences of sepsis, leading to multiorgan dysfunction. The most common organ being affected is the circulatory system.

### *Circulation*

Hypotension due to diffuse vasodilation is the most severe expression of circulatory dysfunction in sepsis. It is probably an unintended consequence of the release of vasoactive mediators, whose purpose is to improve metabolic autoregulation (the process that matches oxygen availability to changing tissue oxygen needs) by inducing appropriate vasodilation. Mediators include vasodilators like prostacyclin and nitric oxide, which are produced by endothelial cells.(8)

Nitric oxide (NO) is believed to play a central role in the vasodilation accompanying septic shock. Inducible NO synthase can be induced by incubating vascular endothelium and smooth muscle with endotoxin. When NO reaches the systemic circulation, it depresses metabolic autoregulation at all of the central, regional, and microregional levels of the circulation. In addition, NO may trigger an injury in the central nervous system that is localized to areas that regulate autonomic control. Another factor that may contribute to the

persistence of vasodilation during sepsis is impaired compensatory secretion of antidiuretic hormone (ADH).(11)

In addition to the diffuse effects on circulation, there are also localised effects. In the central circulation (i.e., heart and large vessels), decreased systolic and diastolic ventricular performance due to the release of myocardial depressant substances is an early manifestation of sepsis. In the regional circulation (i.e., small vessels leading to and within the organs), vascular hypo responsiveness (i.e., inability to appropriately vasoconstrict) leads to an inability to appropriately distribute systemic blood flow among organ systems. As an example, sepsis interferes with the redistribution of blood flow from the splanchnic organs to the core organs (heart and brain) when oxygen delivery is depressed.(11)

The microcirculation (i.e., capillaries) may be the most important target in sepsis. Sepsis is associated with a decrease in the number of functional capillaries, which causes an inability to extract oxygen maximally.

At the level of the endothelium, sepsis induces phenotypic changes to endothelial cells. This occurs through direct and indirect interactions between the endothelial cells and components of the bacterial wall.

In the lung Endothelial injury in the pulmonary vasculature during sepsis disturbs capillary blood flow and enhances microvascular permeability, resulting in interstitial and alveolar pulmonary edema. This creates ventilation-perfusion mismatch and leads to hypoxemia. Such lung injury is prominent during sepsis, likely reflecting the lung's large microvascular surface area. Acute respiratory distress syndrome is a manifestation of these effects.

The other effects seen are liver dysfunction, acute renal failure, and CNS complications including altered sensorium and peripheral neuropathy.

**Table1 -**

Biologic effects of proinflammatory cytokines such as TNF and IL-1(8)
Fever
Hypotension
Acute phase protein response
Induction of IL-6 and IL-8
Coagulation activation
Fibrinolytic activation
Leucocytosis
Neutrophil degranulation and augmented antigen expression (TNF)
Increased endothelial permeability (TNF)
Stress hormone response
Enhanced gluconeogenesis (TNF)

**Insult**

- Severe infection (sepsis)
- Other (SIRS)

↓

Inflammation

↓

Proinflammatory system

↔

Antiinflammatory system

↓

Cellular injury

↓

MODS

↓

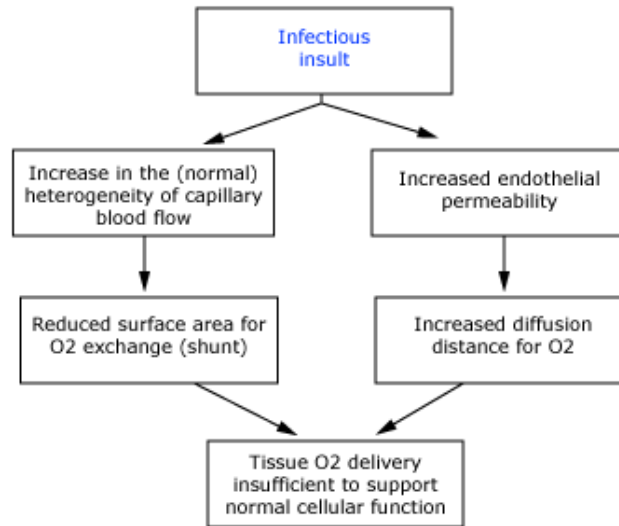
Cellular repair

↓

Recovery

**Figure 1 - Potential outcomes of mediator release in sepsis**





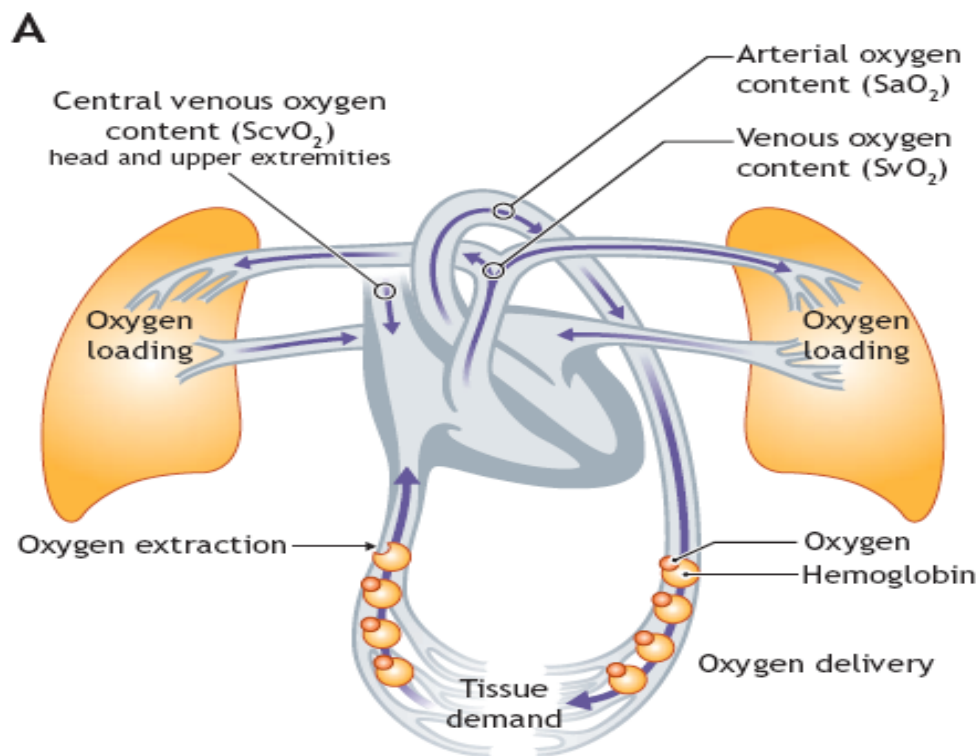
**Decreased oxygen extraction in sepsis**  
**Figure 2**

### *Physiology of Systemic Oxygen Transport and Utilization*

Because microvascular injury leads to decreased oxygen delivery and consumption at the cell and tissue level, the principles of oxygen transport physiology become requisite to an understanding of the pathogenic, diagnostic, and therapeutic implications of global tissue hypoxia. Oxygen is delivered to the tissues as a product of cardiac output and oxygen content (which is a product of haemoglobin oxygen saturation and haemoglobin).

After oxygen is extracted at the tissue level, the remainder returns to the venous circulation. The product of Systemic oxygen delivery and the percentage of oxygen extracted (normally 25%) by the tissues is the systemic oxygen consumption. The balance between systemic oxygen delivery and consumption is reflected by the mixed venous haemoglobin oxygen saturation (SvO<sub>2</sub>). Global tissue hypoxia results when there is an inability of systemic oxygen

delivery to meet the oxygen requirements of the tissues and results in lactic acidosis.(12)



**figure.3 Oxygen transport**

One of the most important events leading to morbidity and mortality in patients with sepsis is the development of cardiovascular insufficiency and resulting global tissue hypoxia. Global tissue hypoxia (or oxygen deprivation), which can occur before the development of hypotension, results in further endothelial activation and generalized inflammation. Global tissue hypoxia develops from multiple mechanisms of cardiovascular insufficiency. These mechanisms include decreased preload, vasoregulatory dysfunction, myocardial depression, increased metabolic demands, and impaired tissue oxygen use resulting from microcirculatory dysfunction and cytopathic hypoxia.(12)(8)

First, although sepsis is commonly characterized as hyper dynamic, some patients may present in the early stages with a decreased preload because of concomitant left ventricular dysfunction and hypovolemia. After fluid resuscitation to normalize filling pressures, compensatory mechanisms of ventricular dilatation and tachycardia permit a transition to a hyper dynamic state or high cardiac output.

Second, even in the presence of a normal or high cardiac output in severe sepsis or septic shock, hypoperfusion abnormalities can still exist. This “distributive shock” refers to a state of either systemic or regional hypoperfusion as a result of derangements in blood flow distribution and loss of vasoregulatory control to the vascular beds.

Third, myocardial depression reflecting a hypodynamic state with low cardiac output, thought to occur as a result of effects of inflammatory mediators, can be the predominant hemodynamic feature in up to 15% of patients presenting with severe sepsis or septic shock and may be especially profound in patients with pre-existing cardiac disease.

Fourth, the inflammatory response accompanying sepsis is also associated with increased metabolic demands, reflected by an increase in splanchnic and total body oxygen consumption. The combination of measuring central venous oxygen saturation (ScvO<sub>2</sub>), which is usually 5% to 7% higher than SvO<sub>2</sub> with very good correlation coefficients, and lactate during initial patient assessment allows for the early recognition of these contributors to cardiovascular insufficiency and global tissue hypoxia that can occur despite the presence of stable vital signs.

Last, in addition to sepsis causing impairment in oxygen delivery, the bioenergetics of cellular oxygen extraction and use or respiration may also be impaired. This cytopathic hypoxia can manifest with a normal or high SvO<sub>2</sub> and lactic acidosis. These derangements

further contribute to the cardiovascular insufficiency and may occur independent of hemodynamic parameters, such as arterial blood pressure.(8)(12)

## **DIAGNOSIS**

To diagnose severe sepsis or septic shock as early as possible, it is necessary to recognise historical, clinical, and laboratory findings that are indicative of infection, organ dysfunction and global tissue hypoxia.

*Infection*, documented or suspected, and some of the following:

### *General variables*

- Fever (core temperature 38.3°C [101.0°F])
- Hypothermia (core temperature 36°C [96.8°F])
- Pulse rate 90 beats/min or 2 SD above the normal value for age
- Tachypnea (respiratory rate 20 breaths/min)
- Altered mental status
- Significant edema or positive fluid balance (20 mL/kg during 24 h)
- Hyperglycaemia (plasma glucose 120 mg/dL or 7.7 mmol/L) in the absence of diabetes

### *Inflammatory variables*

- Leucocytosis (WBC count 12,000/mm<sup>3</sup>)
- Leukopenia (WBC count 4,000/mm<sup>3</sup>)
- Normal WBC count with 10% immature forms
- Plasma C-reactive protein 2 SD above the normal value

- Plasma procalcitonin 2 SD above the normal value

### *Hemodynamic variables*

- Arterial hypotension (SBP 90 mm Hg, MAP 70 mm Hg, or an SBP decrease 40 mm Hg in adults or 2 SD below normal for age)
- SvO<sub>2</sub> < 70%
- Cardiac index of <3.5 L/min/m<sup>2</sup>

### *Organ dysfunction variables*

- Arterial hypoxemia (PaO<sub>2</sub>/FIO<sub>2</sub> <300)
- Acute oliguria (urine output 0.5 mL/kg/h for at least 2 h)
- Creatinine increase 0.5 mg/dL
- Coagulation abnormalities (INR 1.5 or aPTT 60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count 100,000/mL)
- Hyperbilirubinemia (plasma total bilirubin 4 mg/dL or 70 mmol/L)

### *Tissue perfusion variables*

- Hyperlactatemia (2 mmol/L)
- Decreased capillary refill or mottling

SvO<sub>2</sub> can be low (70%) in early sepsis, signifying inadequate oxygen delivery and global hypoperfusion. ScvO<sub>2</sub> has been used as a surrogate of SvO<sub>2</sub>. Hyperlactatemia is not always

accompanied by a low bicarbonate level or increased anion gap, and, thus, the lactate level must also be measured if severe sepsis is suspected. Increased lactate levels among patients admitted to the hospital with infection and upward trends in lactate levels are associated with poor prognosis and may be used to guide response to therapy.

The finding of an elevated serum lactate level ( $>4$  mmol/L), even in the context of normal macrocirculatory markers of perfusion (i.e., cryptic shock), carries a worse prognosis and higher mortality than does a normal ( $<2$  mmol/L) serum lactate level. In these situations, hyperlactemia indicates on-going tissue hypoperfusion due to misdistribution of flow in the microcirculation even after resuscitation and normalization of the macrocirculation.(13)

## **EARLY HEMODYNAMIC OPTIMISATION**

A goal-directed hemodynamic resuscitation of severe sepsis or septic shock includes a systematic approach to restoration of systemic oxygen delivery through a manipulation of preload (volume), afterload (blood pressure), and contractility (stroke volume) to preserve effective tissue perfusion while avoiding excessive increases in myocardial oxygen consumption (i.e., tachycardia) and maintaining coronary perfusion pressure.

Recently, a trial of early hemodynamic resuscitation to normal physiologic parameters, or early goal-directed therapy, was conducted in ED patients with severe sepsis or septic shock and revealed a significant mortality reduction. Early goal-directed therapy is an algorithmic approach to hemodynamic optimization and resolution of global tissue hypoxia within the first 6 hours of disease presentation. The strategy targets normal oxygen delivery by optimizing preload, afterload, oxygen content, and contractility to achieve a balance between tissue oxygen delivery and consumption (guided by central venous pressure, mean arterial

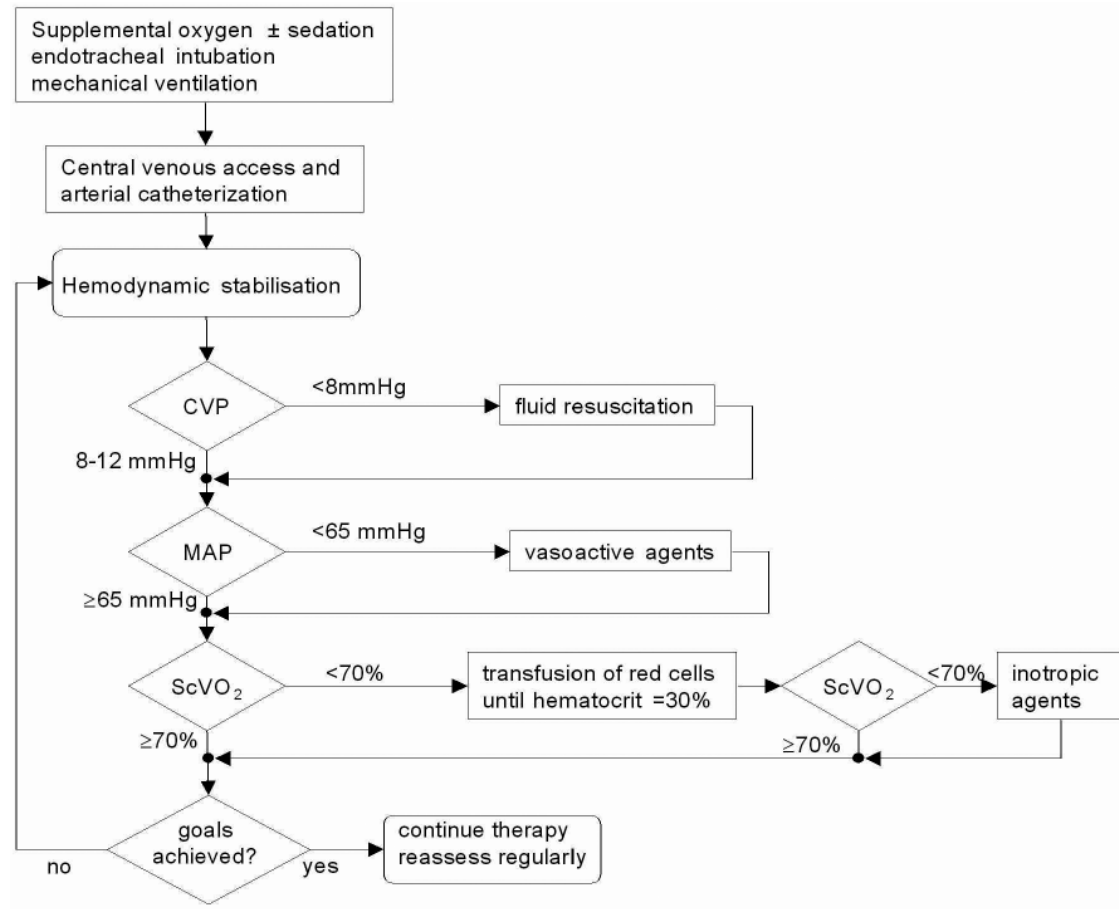
pressure, and ScvO<sub>2</sub> monitoring). Specifically, patients are treated by fluid resuscitation with either crystalloid or colloid to achieve a central venous pressure goal of 8 to 12 mm Hg, vasoactive agents to achieve a mean arterial pressure goal of 65 to 90 mm Hg, blood transfusion to a hematocrit level greater than 30%, inotrope therapy, and intubation, sedation, and paralysis as necessary to achieve a ScvO<sub>2</sub> of greater than 70% as measured by continuous central venous oxygen saturation monitoring.(12)(8)

Rivers et al examined efficacy of early goal-directed therapy in 263 patients with infection associated with hypotension after a fluid bolus or serum lactate level greater than or equal to 4 mmol/L who were randomly assigned to receive standard resuscitation or early goal-directed therapy (133 control versus 130 early goal-directed therapy) in the emergency department before ICU transfer.(14)(15)(16)

*The specific procedures to institute early goal directed therapy are the following.*

- 1) Hemodynamic monitoring
- 2) Volume therapy
- 3) Vasoactive agents
- 4) Increasing oxygen carrying capacity
- 5) Inotropic therapy
- 6) Decreasing oxygen consumption

## FLOW CHART FOR THE EARLY GOAL DIRECTED THERAPY FOR THE EARLY RESUSCITATION OF PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK(12)



**Figure 4**

### *Resuscitation end point s*

Trends of vital signs are not sufficient endpoints to determine an adequate response to therapy. Rady et al showed that 31 of 36 patients presenting with shock and resuscitated to normal vital signs continued to have global tissue hypoxia, as evidenced by decreased ScvO<sub>2</sub> and increased lactate levels. A post hoc analysis of the early goal-directed therapy study in



patients with mean arterial pressure greater than 100 mm Hg showed that control patients with persistently abnormal ScvO<sub>2</sub> and lactate levels at 6 hours had a significantly higher mortality rate compared with the early goal-directed therapy patients whose values had reached therapeutic goals (60.9% versus 20.0%, P.05). Other studies have also showed that a persistently high lactate is associated with increased mortality. Therefore, continuous ScvO<sub>2</sub> and serial lactate measurements during resuscitation may help identify patients requiring continued intensive therapy.(17)(8)

## **MICROCIRCULATION**

The micro-circulation is endowed with certain peculiar characteristics. First and foremost, the microcirculation is heterogenous with regard to rheologic and resistive properties in various organs and within the organ itself . Heterogeneity of flow helps to supply adequate oxygen to tissues based on their metabolic demands. However, it also leads to microcirculatory units with unfavourable rheologic and or resistive properties, making them weaker and thus more vulnerable to damage by hypoxia as encountered during sepsis. Secondly, in almost all vascular beds, there is a longitudinal and radial oxygen gradient such that the capillary pO<sub>2</sub> and haemoglobin saturation are significantly lower than arterial values.

This results from oxygen unloading from arterial network to tissues, and the intrinsic oxygen consumption of vessel wall to sustain endothelial functions and vascular tone. These properties again make the exchange segment more prone to hypoxic damage. The microvascular haematocrit is lower than the systemic haematocrit, and is also heterogeneously distributed . This decrease is due to the Fahreus effect that induces axial

migration of erythrocytes near the centre of vessels, resulting in differential erythrocyte and plasma velocities, and a dynamic decrease in intravascular haematocrit. The end result of all the above characteristics is a heterogeneity of blood flow and oxygen delivery in the microcirculation, resulting in vulnerable units prone to hypoxic damage.(11)(18) (19)

### *Pathophysiology of microcirculation in sepsis*

The inflammatory mediators that herald sepsis, and the changes they induce in the macrohaemodynamics i.e., blood pressure, heart rate and oxygen extraction are well known. These are the changes induced in the microcirculation by sepsis. "Five to fifteen minutes after its (endotoxin) intravenous administration, there were strong waves of contraction along the small arteries, arterioles, and metaarterioles. These could arrest flow and last for several minutes. There would afterwards be a phase of dilation, followed by a strong contraction. As time went on, the phases of relaxation became more prominent until preagonally there was a general and permanent vasodilation. The circulation would slow progress until death." This early description of response of microvessels to endotoxin in guinea pig and mouse mesentery demonstrates the immediate arteriolar vasoconstriction response to endotoxin followed by the subsequent phases of changing microvascular tone and ultimate cardiovascular collapse.(20)(13)

The release of endotoxin or proinflammatory cytokines initiates a cascade of cellular and mediator changes in sepsis. The cornerstone of impaired homeostasis in sepsis is an inflamed microcirculation. It is clogged with microthrombi and leaks extensively and the central role in this microcirculatory dysfunction is in turn played by the endothelium.

Activation of the coagulation cascade leading to intravascular thrombosis is also a result of the damaged endothelium that starts liberating procoagulant factors. Besides these alterations, the endothelium also fails to perform its regulatory functions, and its nitric oxide (NO) system is severely disturbed. There is a heterogenous expression of inducible nitric oxide synthase (iNOS) in the endothelium of different areas of organ beds. Areas that lack iNOS have less NO induced vasodilation and become underperfused resulting in pathological shunting of blood flow..

The endothelium is not the only component of microcirculation to be altered. The arterioles are hyporesponsive to vasoconstrictors and vasodilators despite the elevated levels of catecholamines[[4](#)], perfused capillaries are reduced in number, and venules are obstructed by the sequestered neutrophils. In the capillaries, besides a decreased density, there also occurs increased heterogeneity and an increase in the proportion of stopped and intermittently perfused capillaries.

This shut-down of the vulnerable microcirculatory units in the organ beds promotes the shunting of blood and hence oxygen, from arterial to venous compartment leaving the microcirculation hypoxic, along with a decrease in oxygen extraction. The local microcirculatory partial pressure of oxygen drops below the venous oxygen pressure. This difference has been termed the "pO<sub>2</sub> gap" and is an indicator of the severity of functional shunting . The systemic manifestation of this pathologic shunting is seen as a deficit of oxygen extraction by tissues with an apparently normal delivery, and raised venous pO<sub>2</sub> , lactate, and gastric CO<sub>2</sub> , levels. In addition, the blood flow regulation of microcirculation is severely disrupted.

## *Assessment of microcirculation*

Till date, there is no single objective gold standard to assess the microcirculation. In clinical practice, microcirculatory perfusion has been traditionally judged by the colour, capillary refill and temperature of the distal parts of the body (i.e., finger, toes, earlobes and nose). Amongst the investigational modalities available to assess microcirculation, both indirect indicators as well as direct techniques exist, even though any single objective reliable method is still not recognized. Indirect techniques involve measurement of 'downstream' global derivatives of microcirculatory dysfunction such as lactate, carbondioxide, and venous oxygen saturation. The direct imaging of microcirculatory perfusion seems a superior approach to assessment of microcirculation.

Measurement of serum lactate levels provides a marker of global tissue hypoxia in the host, and its prognostic value for predicting survival in shock from various causes in animal models and humans has been well established.

Hemodynamic parameters, usually used to assess the perfusion of organs and tissues, like arterial blood pressure, heart rate, urine output and blood gases can be normal in the presence of tissue hypoxia and cannot rule out imbalances between global oxygen supply and demand. Mixed venous oxygen saturation (SvO<sub>2</sub>) is a sensitive indicator of the adequacy of whole-body tissue oxygenation. However, it requires the placement of a pulmonary artery catheter, which is an invasive procedure with the possibility of numerous complications and is increasingly questioned due to the lack of evidence that it improves outcome. Central venous oxygen saturation (ScvO<sub>2</sub>) requires the insertion of a central venous catheter, which is routinely used in most critically ill patients.

It can be used as a surrogate for mixed venous oxygen saturation because the changes and trends of both variables parallel each other. Both variables are used extensively in the treatment of patients with severe sepsis, shock and trauma. In combination with other hemodynamic and biochemical parameters, they have diagnostic and prognostic value and allow for rational treatment of critically ill patients.

## **VENOUS OXIMETRY**

### *Physiology and pathophysiology of venous oxymetry*

Venous oxymetry reflects the balance between oxygen supply or delivery (DO<sub>2</sub>) and oxygen consumption (VO<sub>2</sub>). DO<sub>2</sub> is dependent on cardiac output (CO) and oxygen content in arterial blood (CaO<sub>2</sub>) which is the sum of oxygen bound to haemoglobin product of haemoglobin concentration (Hb) and arterial O<sub>2</sub> saturation (SaO<sub>2</sub>) and physically dissolved oxygen (PaO<sub>2</sub>), according to the following formulas:(21)

$$DO_2 = CO \times CaO_2$$

$$CaO_2 = (Hb \times 1,36 \times SaO_2) + (PaO_2 \times 0,0031)$$

The amount of physically dissolved oxygen is small and can be neglected for practical purposes. Thus, oxygen delivery is defined mostly by CO, Hb and SaO<sub>2</sub>. Clinical conditions that can affect DO<sub>2</sub> are low cardiac output, anemia and hypoxia (decreased DO<sub>2</sub>) and high cardiac output or CaO<sub>2</sub> which increase DO<sub>2</sub>. Oxygen demand or whole-body oxygen consumption (VO<sub>2</sub>) can be expressed by the product of CO and arteriovenous O<sub>2</sub> content difference (CaO<sub>2</sub> – CvO<sub>2</sub>) which is known as the Fick principle:

$$VO_2 = CO \times (CaO_2 - CvO_2) \text{ or rearranged}$$

$$CvO_2 = CaO_2 - VO_2 / CO$$

That means that mixed venous oxygen content ( $CvO_2$ ) reflects the relation between whole body oxygen consumption and cardiac output under conditions of constant  $CaO_2$ .  $CvO_2$  can also be expressed by the equation:

$$CvO_2 = (Hb \times 1.36 \times SvO_2) + (PvO_2 \times 0.0031)$$

As physically dissolved oxygen can be neglected, the principal determinants of  $CvO_2$  are Hb and  $SvO_2$ . Since Hb is usually constant in a certain period of time,  $CvO_2$  is mostly determined by  $SvO_2$ .  $SvO_2$  is inversely related to the  $VO_2 / CO$  ratio. Clinical conditions that can affect  $VO_2$  are stress, pain, hyperthermia and shivering or analgesia, sedation, mechanical ventilation and hypothermia which decrease  $O_2$  consumption.

Oxygen delivery and consumption are linked by a simple relationship:

$$VO_2 = DO_2 \times ERO_2 \text{ or}$$

$$ERO_2 = VO_2 / DO_2$$

where  $ERO_2$  represents oxygen extraction ratio as a percentage. Normally  $ERO_2$  is about 25% which means that 25% of delivered oxygen is taken up by tissues and 75% returns to the lungs.(22)(18)

$ERO_2$  is inversely related to  $SvO_2$ , which is shown in the equation:

$$SvO_2 = 1 - ERO_2$$

Therefore, normal ERO<sub>2</sub> of 25% corresponds to SvO<sub>2</sub> of 75%, and ERO<sub>2</sub> of 60 % matches SvO<sub>2</sub> of 40%. Under normal conditions VO<sub>2</sub> is independent of DO<sub>2</sub> because tissues can meet their needs for oxygen by increasing extraction. When this compensation is exhausted at critical DO<sub>2</sub>, VO<sub>2</sub> becomes dependent of DO<sub>2</sub>. Anaerobic metabolism occurs and lactates begin to rise.(23)(24)

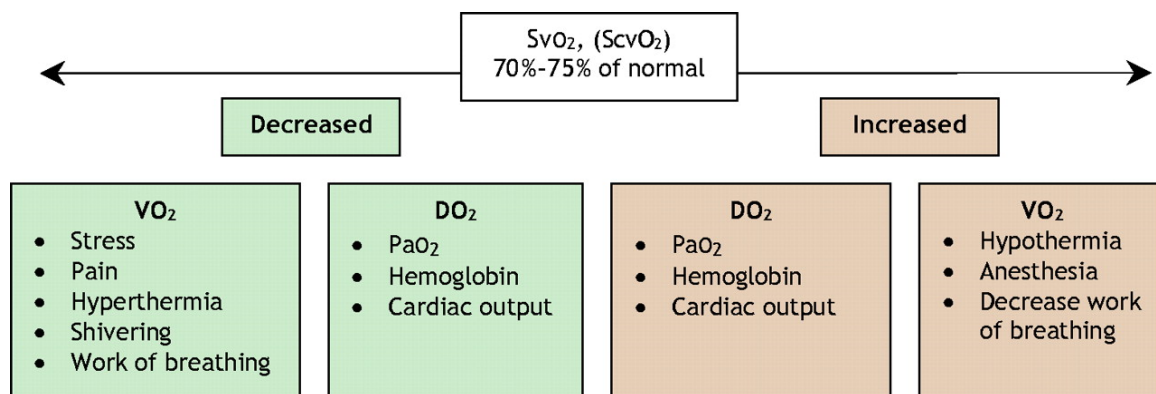
Oxygen delivery and consumption vary during physiological (exercise) and clinical conditions. The normal cardiovascular response to increasing VO<sub>2</sub> is to increase ERO<sub>2</sub> and cardiac output. SvO<sub>2</sub> normally decreases during exercise because the increased cardiac output cannot match completely the increased O<sub>2</sub> demand. Therefore, a drop in SvO<sub>2</sub> does not necessarily mean that tissue hypoxia is occurring but represents increased metabolic stress. The extent of the SvO<sub>2</sub> drop denotes the magnitude of the stress. In a healthy person anaerobic metabolism usually occurs when SvO<sub>2</sub> drops below 40% for a substantial period of time. In patients with severe heart disease the ERO<sub>2</sub> is increased at rest and they can live with SvO<sub>2</sub> in the low range without apparent hypoxia because they have adapted to hypoxia (rightward shift of oxyhemoglobin dissociation curve ,adaptation of peripheral microvasculature). In a septic patient misdistribution of blood flow and the disturbance of mitochondrial oxygen utilization may cause anaerobic metabolism in the presence of normal or even high SvO<sub>2</sub>. In that case blood lactate levels and base deficit will be high.

The normal values of SvO<sub>2</sub> are considered to be between 60 and 80%. Examples from above show that SvO<sub>2</sub> values should be interpreted carefully in the context of a wider clinical and biochemical picture.

Venous oximetry can reflect the adequacy of tissue oxygenation only if the tissue is still capable of extracting O<sub>2</sub>. In the case of arteriovenous shunting on the microcirculatory level or cell death, SvO<sub>2</sub> and ScvO<sub>2</sub> may not decrease or even show elevated values despite severe

tissue hypoxia. As demonstrated in patients after prolonged cardiac arrest, venous hyperoxia with an ScvO<sub>2</sub> higher than 80% is indicative of impaired oxygen use.

While measurement of SvO<sub>2</sub> requires the insertion of a pulmonary artery catheter, measurement of ScvO<sub>2</sub> requires only central venous catheterization. ScvO<sub>2</sub> directed early goal-directed therapy improves survival in patients with septic shock who are treated in an emergency department. However, ScvO<sub>2</sub> values may differ from SvO<sub>2</sub> values, and this difference varies in direction and magnitude with cardiovascular insufficiency. ScvO<sub>2</sub> should not be used alone in the assessment of the cardiocirculatory system but combined with other cardio-circulatory parameters and indicators of organ perfusion such as serum lactate concentration and urine output.(25)



**Figure 5 Causes for deranged venous oxygen content(SvO<sub>2</sub>)**



## **CLINICAL APPLICATION OF SCVO2(12)**

### ***1. SEVERE SEPSIS AND SEPTIC SHOCK***

Severe sepsis and septic shock are frequently complicated by the development of the multiple organ dysfunction syndrome(MODS). Tissue hypoxia is believed to be one of the most important mechanisms for the onset of MODS.

However, treatment concepts favoring the achievement of a maximum O<sub>2</sub> delivery have proven to be of no benefit in these patients. Furthermore, it is very difficult to define goals for cardiovascular resuscitation in these patients. In this context, Rivers and coworkers demonstrated in patients with severe sepsis or septic shock that an early and aggressive resuscitation guided by the ScvO<sub>2</sub> in addition to central venous pressure and mean arterial pressure reduced the 28 day mortality rate from 46.5% to 30.5% (p=0.009) .

This concept was called Early Goal Directed Therapy (EGDT). Compared to the conventionally treated group, the EGDT group received more fluids, more frequently required dobutamine, and more blood transfusion during the first 6 hours.

This resulted in a faster and better improvement of organ function in the EGDT group. The application of EGDT in the early resuscitation of patients with severe sepsis or septic shock is recommended in current guidelines. In a multi centre study of ScvO<sub>2</sub> as a predictor of mortality in sepsis done by Pope et al showed that both the hypoxia and the hyperoxia group had significantly higher mortality than the normoxia group. In multivariate analysis for initial ScvO<sub>2</sub> the hyperoxia group was associated with increased mortality but not the hypoxia group. Similarly retrospective analysis done in patients with septic shock by Julien et al suggested that the ScvO<sub>2</sub> max was 85% in nonsurvivors compared with 79% in

the survivors(p value = 0.009) raising concerns about high levels of ScvO<sub>2</sub> in sepsis patients; the probable cause being impaired oxygen extraction.

## ***2. SEVERE TRAUMA AND HEMORRHAGIC SHOCK***

The care of severely traumatized patients is defined by early and aggressive resuscitation followed by early surgical intervention. Patients with shock, that have been haemodynamically stabilized according to vital signs such as heart rate, blood pressure, and central venous pressure, had an insufficient ScvO<sub>2</sub> in 50% of cases .

Those patients with a ScvO<sub>2</sub> <65% were in need of further intervention and demonstrated prolonged cardiac dysfunction and elevated lactate levels. Although there has been no study, which investigated the validity of ScvO<sub>2</sub> to guide haemodynamic stabilization in polytraumatized patients, there is good evidence from patients with severe sepsis or septic shock that the ScvO<sub>2</sub> is a good parameter in the resuscitation of haemodynamically unstable patients.

In patients who are initially haemodynamically stable after trauma, a ScvO<sub>2</sub> below 65% was able to detect those patients who suffered from blood loss and were in need of blood transfusion.

## **POLYTRAUMA**

Organ and tissue damages caused by a trauma impact lead to the development of systemic inflammatory response syndrome (SIRS). The local and systemic release of inflammation mediators produces oxidative stress, capillary leakage, microcirculatory disturbances, metabolic alteration, imbalance of pro- and anti-inflammatory mechanisms, ischaemia or reperfusion injury, coagulation disturbances. In major trauma, occult tissue hypoperfusion within the first 24 hours after event precedes multiple organ dysfunction syndrome(MODS). Immediate and early trauma deaths are determined by primary brain injuries, or significant blood loss (haemorrhagic shock), while late mortality is caused by secondary brain injury and host defence failure.(26)

First hits (hypoxia, hypotension, organ and soft tissue injuries, fractures), as well as second hits (e.g. ischaemia or reperfusion injuries, compartment syndromes, operative interventions, infections), induce a host defence response. This is characterized by local and systemic release of pro-inflammatory cytokines, arachidonic acid metabolites, proteins of the contact phase and coagulation systems, complement factors and acute phase proteins, as well as hormonal mediators: it is defined as systemic inflammatory response syndrome (SIRS), according to clinical parameters. However, in parallel, anti-inflammatory mediators are produced (compensatory anti-inflammatory response syndrome (CARS). An imbalance of these dual immune responses seems to be responsible for organ dysfunction and increased susceptibility to infections(27)

Endothelial cell damage, accumulation of leukocytes, disseminated intravascular coagulation (DIC) and microcirculatory disturbances lead finally to apoptosis and necrosis of parenchymal cells, with the development of multiple organ dysfunction syndrome (MODS), or multiple organ failure (MOF). Despite the unquestionable usefulness of routinely

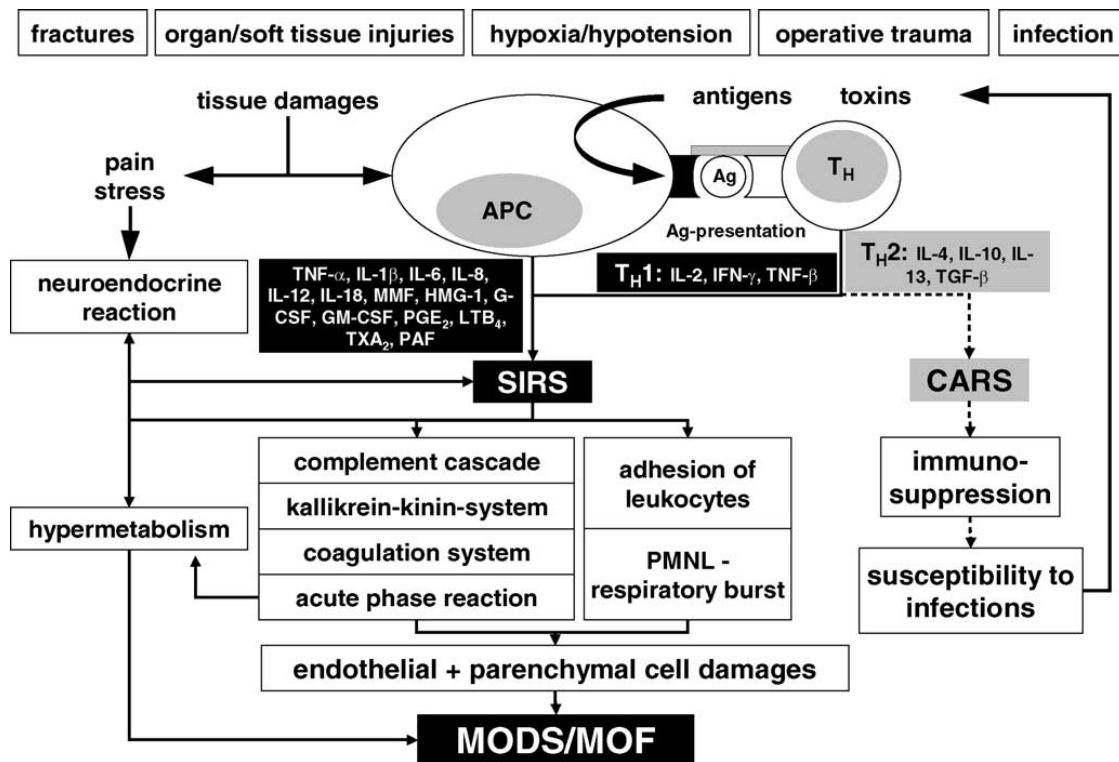
monitoring of hemodynamic parameters, such as arterial lactate, central venous pressure, blood pressure, heart rate, urinary volume, hypoxia may exist despite normal clinical values.

Continuous monitoring of central venous oxygen saturation (ScvO<sub>2</sub>) has been proposed as an indicator of tissue hypoperfusion. Although the reliability of ScvO<sub>2</sub>, compared with mixed venous oxygen saturation (SvO<sub>2</sub>), is still under discussion, particularly under shock conditions, the prognostic importance of low level ( $\leq 65\%$ ) of ScvO<sub>2</sub> has been highlighted in severe sepsis, myocardial infarction, cardiac failure, and trauma. Moreover, ScvO<sub>2</sub> can be easily monitored with a central venous line, whereas SvO<sub>2</sub> requires a pulmonary artery catheterization.

No studies have evaluated ScvO<sub>2</sub> in patients affected by major trauma so far. The most numerous and extensive studies on ScvO<sub>2</sub> optimization have been performed on septic patients. The pathogenic changes following major trauma include SIRS, oxidative stress, capillary leakage, metabolic alterations, and diffuse tissue hypoxia as a result of circulatory abnormalities. This pathophysiological process is somehow very similar with what observed in septic patients, although sepsis presents a different aetiology, evolution and possibility to be treated with antibiotics.

Considering the good evidence in patients with severe sepsis or septic shock, the use of ScvO<sub>2</sub> to guide hemodynamic optimization in polytraumatized patients would merit to be adequately investigated.

## Host defence response after trauma.



**Figure 6**

APC: antigen presenting cells. TH, T-helper cells (lymphocytes); SIRS, systemic inflammatory response syndrome; CARS, compensatory anti-inflammatory response syndrome; PMNL, polymorphonuclear leukocytes; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure.

## Oxidative stress and capillary leakage.

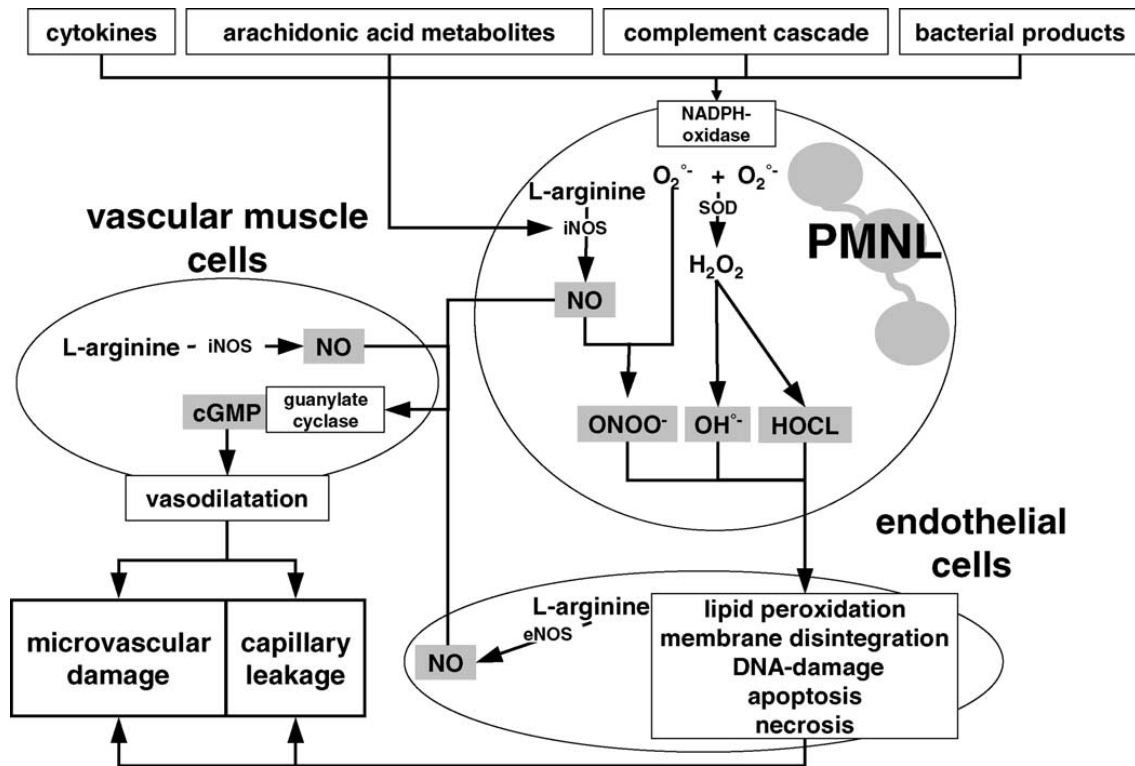


Figure 6

Activated polymorphonuclear leukocytes (PMNL) release reactive oxygen (ROS) and reactive nitrogen species (RNS). These metabolites in combination with proteases are responsible for endothelial cell damages and the development of a capillary leakage.

## **APACHE II SCORING**

APACHE II – Acute Physiology and Chronic Health Evaluation System is a severity of disease classification which was first validated and used by Knaus W A et al and published in the Critical Care Medicine Journal in 1985. APACHE II uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. The physiological measurements include the temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium levels, serum potassium level, serum creatinine (with or without acute renal failure), haematocrit, the total count and the Glasgow Coma Score.(28)

The score ranges from 0 to 71 with a worsening outcome as the score rises. When APACHE II scores are combined with an accurate description of disease, it can be used to prognosticate acutely ill patients and will also guide investigators to compare new modes of treatment.

Another use of the APACHE II score is that it can be used to evaluate the use of hospital resources and compare between intensive care units as to the efficacy of care.

APACHE II has been used universally in many clinical trials since it provides a consistency between different groups. An objective scoring system such as the APACHE II score, allows audits of different units or the same unit with historical controls, and comparisons of different treatment modalities in those with similar severity of illnesses. In the current environment of escalating medical costs the APACHE II scores may allow us to restrict intensive care to those most at need, and provide a gauge of illness for deciding how aggressive management should be. The popularity in the use of the APACHE II score is that it is simple to use and there is available software to simplify analysis.

**APACHE II score = (acute physiology score) + (age points) + (chronic health points)(29)**

***Acute Physiology Score***

1 = Rectal temp (C)

2 = Mean arterial pressure (mmHg)

3 = Heart rate (bpm)

4 = Respiratory rate (bpm)

5 = Oxygen delivery (ml/min)

6 = PO<sub>2</sub> (mmHg)

7 = arterial pH

8 = Serum sodium (mmol/l)

9 = Serum potassium (mmol/l)

10 = Serum creatinine (mg/dl)

11 = Haematocrit (%)

12 = White cell count (10<sup>3</sup>/ml)



	+4	+3	+2	+1	0	+1	+2	+3	+4
1	>41	39-40.9		38-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
2	>160	130-159	110-129		70-109		50-69		<49
3	>180	140-179	110-139		70-109		55-69	40-54	<39
4	>50	35-49		25-34	12-24	10-11	6-9		<5
5	>500	350-499	200-349		< 200				
6					> 70	61-70		55-60	< 55
7	>7.7	7.6-7.69		7.5-7.59	7.3-7.49		7.25-7.3	7.15-7.2	< 7.15
8	>180	160-179	155-159	150-154	130-149		120-129	111-119	<110
9	>7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
10	>3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
11	>60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
12	>40		20-39.9	15-19.9	3-14.9		1-2.9		< 1

### ***Age Points***

Age	Points
<44	0
45-54	2
55-64	3
65-74	5
>75	6

### ***Chronic Health Points***

History of severe organ insufficiency	Points
Non-operative patients	5
Emergency postoperative patients	5
Elective postoperative patients	2

Organ insufficiency or immunocompromised state must have preceded the current admission

*Immunocompromised if:*

- Receiving therapy reducing host defences (immunosuppression, chemotherapy, radiation therapy, long term steroid use, high dose steroid therapy) or
- Has a disease interfering with immune function such as malignant lymphoma or leukaemia.

*Hepatic insufficiency if:*

- Biopsy proven cirrhosis
- Portal hypertension
- Episodes of upper GI bleeding due to portal hypertension
- Prior episodes of hepatic failure, coma or encephalopathy

*Cardiovascular insufficiency if:*

- New York Heart Association Class IV

*Respiratory insufficiency if:*

- Severe exercise restriction due to chronic restrictive, obstructive or vascular disease,
- Documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension
- Respirator dependency

*Renal insufficiency if:*

- On chronic dialysis

# PATIENTS AND METHODS

## SETTINGS:

The study was done in the Surgical Intensive Care Unit (SICU) of Christian Medical College Hospital, Vellore which is a 2000 bedded tertiary care hospital serving about 90,000 inpatients and 1.5 million outpatients annually. The study was done among 86 patients who fulfil the inclusion criterion with a diagnosis of sepsis and or polytrauma from May 2011. They were enrolled in the study after obtaining written consent wherever possible. Where this was not possible, an assent would be obtained from the next of the kin in a language comprehensible to them. The protocol received approval from the Institutional Review Board of Christian Medical College, Vellore and was funded by the fluid research fund of the Christian Medical College.

## ELIGIBILITY:

Patients between age 18 to 80 years admitted to SICU and SHDU with a diagnosis of sepsis and poly trauma.

## EXCLUSION CRITERIA:

1. Age less than 18 years or above 80 years
2. Pregnant mothers

3. Known cases of chronic lung disease
4. Known cases of cardiac disease – moderate to severe left ventricular failure, Intra and extra cardiac shunts.
5. Liver failure – acute / chronic
6. Patients recruited in another trial
7. Patients with central venous catheter whose tip is not in the superior vena cava.

The sample size was calculated based on mortality of 30% associated with sepsis and trauma from previous studies.

$$P=30\%$$

$$Q=100-30\%=70\%(\text{power of the study})$$

$$D2=7 \times 7 (+/- 5)$$

$$\text{Sample size} = 4 \times p \times q / d^2$$

$$= 4 \times 30 \times 70 / 7 \times 7$$

$$= 170$$

Thus arriving to a sample size of 170. The study was censored at 86 subjects in order to meet the deadline for submission of thesis.

A blood sample from a central venous catheter, whose tip is located in the superior venacava was collected after ensuring that the systemic oxygen saturation on the pulse-oximeter is more than 93 % according to the unit protocol. Simultaneously, an arterial blood sample was obtained for analysis. A similar set of central venous and arterial sample were collected for

analysis 6 hours after ICU admission. Severity of illness scoring (APACHE II) was recorded 24 hours after hospital admission. The patients were subjected to the standard treatment. During the treatment period, need and duration of inotropic support, ventilatory support, renal replacement therapy were collected in a data sheet by the investigators or the doctors in charge. ICU mortality and 28 day in hospital mortality were recorded.

*Variables of interest were ScvO<sub>2</sub>, Blood Lactate and base excess.*

**Scvo<sub>2</sub>** was measured by doing a venous blood gas analysis one at the time of admission to SICU and the other after 6 hours and ScvO<sub>2</sub> levels were stratified into the clinically meaningful groups of low (ScvO<sub>2</sub> 0 < 65%), normal (65-75%), and supra-normal (>75%). These thresholds were selected apriori.

**Lactate and base excess** were measured by doing an arterial blood gas analysis similarly one at admission and one after 6 hours. The lactate values of 0.5 to 2.0mmol/l were considered normal.

The base excess of -3 to +3 was considered normal. The three groups namely the low, normal and supra-normal SCVO<sub>2</sub> were compared. The oxygen extraction was calculated based on the arterial and venous oxygen content which could be calculated with the values obtained in the blood gas analysis.

## STATISTICAL METHODS:

- 1) The mortality rate was calculated with 95% confidence interval.
- 2) Association between various factors (ScvO<sub>2</sub>, lactate, base excess) and mortality was assessed using chi square tests.
- 3) Multivariate logistic regression analysis were performed to identify independent predictors of mortality.
- 4) ORS with 95% confidence interval was calculated.

The mortality rates for the respective groups were compared to determine statistical significance using Fisher's exact test, with alpha set at 0.017 using a Bonferonni correction ( $0.05/3 = 0.017$ ) to adjust for multiple comparisons. We also performed a univariate analysis of the covariates that we collected using fisher's exact test, followed by a stepwise logistic regression (both automated and by-hand) retaining significance covariates ( $p < 0.05$ ), to control for confounders in evaluating the relationship between ScvO<sub>2</sub> and mortality.

# RESULTS

A total of 86 patients who met the criteria for ICU admission were enrolled in the study.

There were almost equal number of patients between 18-45 years and above 45 years with mean age of 43.85 (SD16.293) . 32.56% were women and 67.44 were men. 88% were admitted with a diagnosis of sepsis and 12% had diagnosis of poly trauma. The common co-morbidities were diabetes (17%), hypertension (4%) and chronic kidney disease (5.81%). The overall mortality for all patients was 11.63% (10/86 patients). The mean APACHE II score was 15.05 with minimum value of 5 and maximum value of 32.

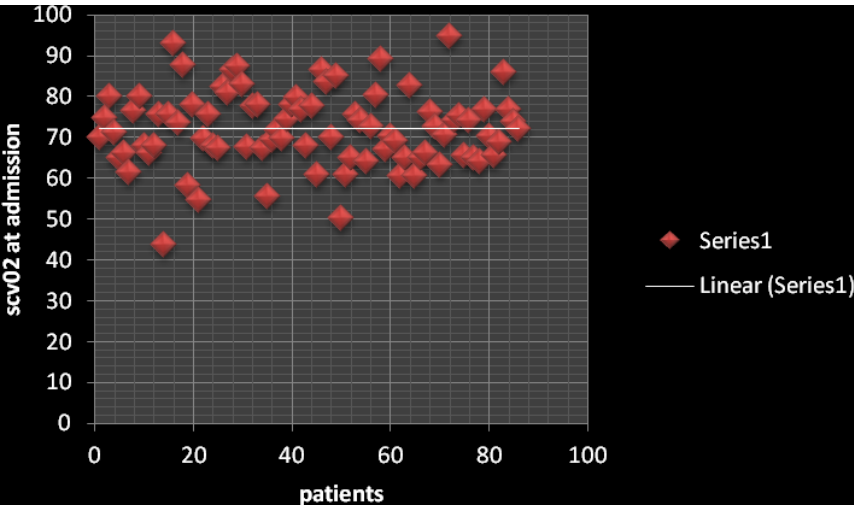
		SCVO2		
		HYPOXIA (<60)	NORMOXIA (60-75)	HYPEROXIA (75.1-100)
GENDER	MALE	9	29	24
	FEMALE	4	11	9
MORTALITY	YES	1	3	6
	NO	12	37	27
AGE (years)	MEAN	43	42	<b>55</b>
APACHE II	MEAN	14	14.15	15.934

**Table 2- Baseline data**



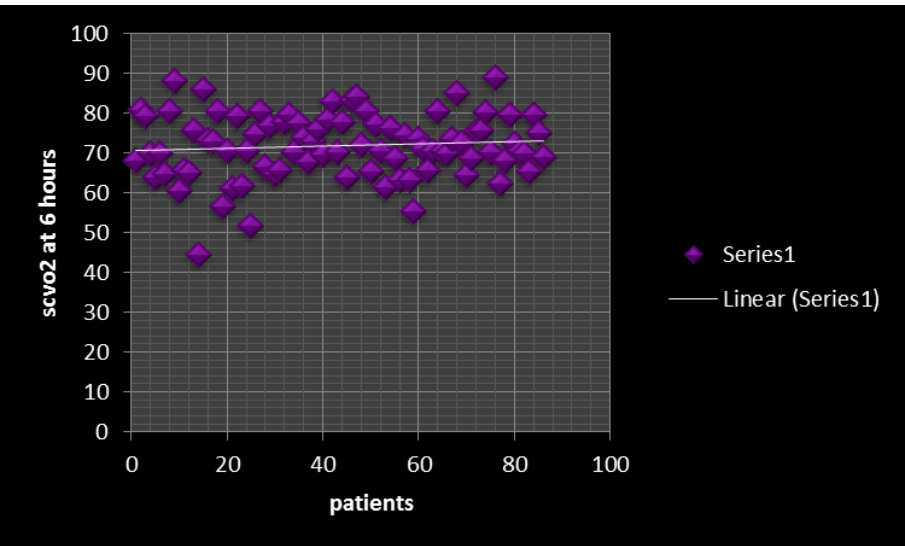
The mean SCVO2 at admission was 72.16 with a minimum of 44 and maximum value of 95.

The plot below depicts the distribution of the SCVO2 values.



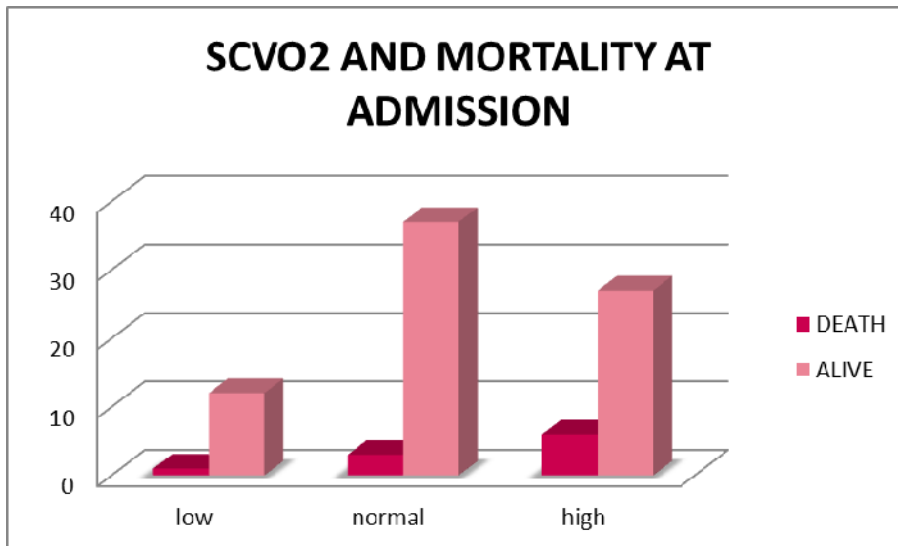
**Figure.8- Distribution of SCVO2 at admission.**

A similar pattern with mean of 72.2 and minimum value of 45 and maximum of 85 was seen 6 hours after ICU admission as in fig.9



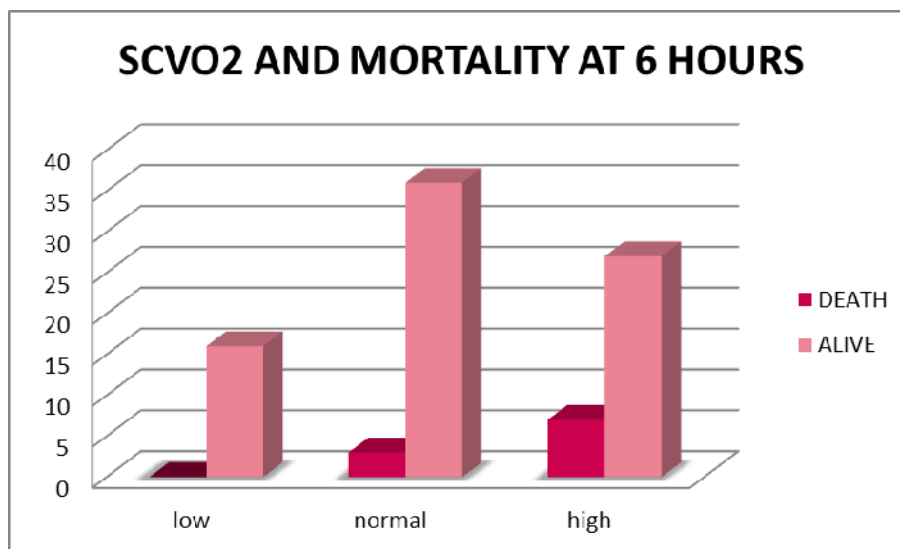
**Figure.9 - Distribution of SCVO2 6 hours after ICU admission.**

Next we evaluated the mortality related to SCVO<sub>2</sub> values at admission to the ICU and to 6 hours after admission. At admission 15% had hypoxia (low SCVO<sub>2</sub>) with a mortality of 7.69% (1/13) and 46% had normoxia with a mortality of 7.65% (3/40) and 38% had hyperoxia (high SCVO<sub>2</sub>) with a mortality of 18.8% (6/33). After 6 hours of ICU admission, the mortality was nil in the hypoxia group, 7.76% in the normoxia group and 22.58% in the hyperoxia group. The mean SCVO<sub>2</sub> at admission in the alive group was 71.65 (CI of 69.53-73.76) and in the mortality group was 76.44 (CI of 70.07-82.81). These values were almost same after 6 hours of ICU admission. Similarly mean APACHE II score in the patients who survived was 14.08 and was 22.30 in the patients who did not survive.



**Figure-10**

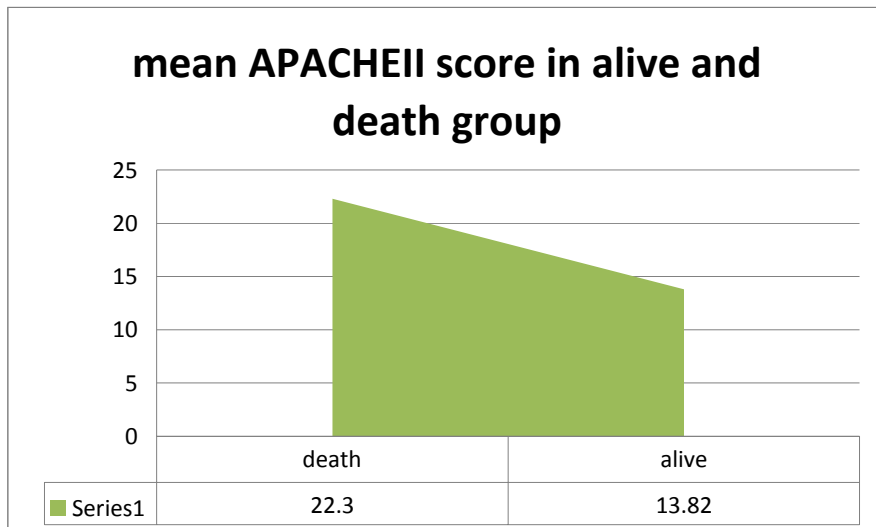
**Correlation of ScvO<sub>2</sub> to mortality at admission**



**Figure -11. Correlation of ScvO2 to mortality after 6 hours**

In figure 10 and figure 11 graphically though it shows that hyperoxia group has a higher mortality statistically its not significant.

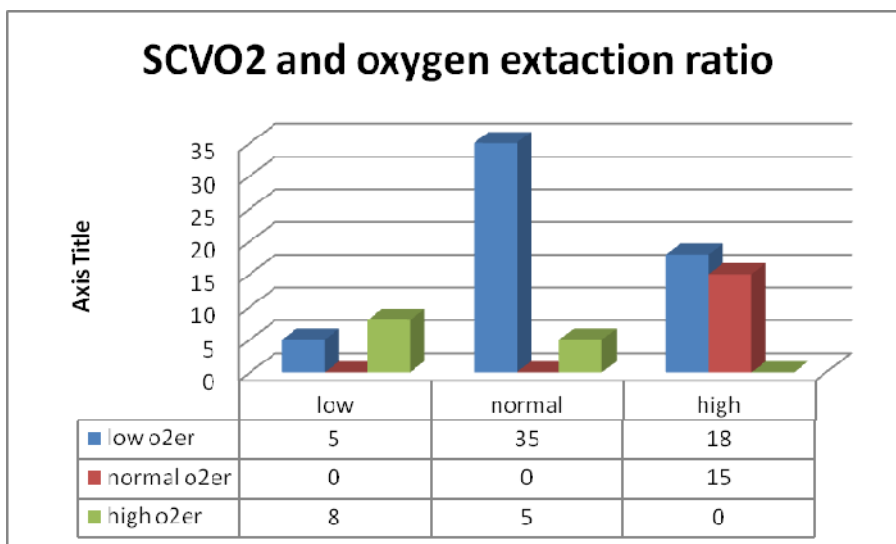
When compared to the normoxia, the mortality in the hyperoxia group was 2.422 times higher though not statistically significant. The hypoxia group had 1.0256 times more likelihood of mortality compared to the normoxia group. When the hypoxia group was compared with the hyperoxia group the risk ratio for mortality was 2.36 times more in the hyperoxia group though the p value was not significant. This is probably due to the reason that only 86 patients were recruited against the planned 170 due to time constraints and that the study is ongoing and the results may become significant when all the patients are recruited.



**Figure -12. Correlation of APACHE II score and mortality**

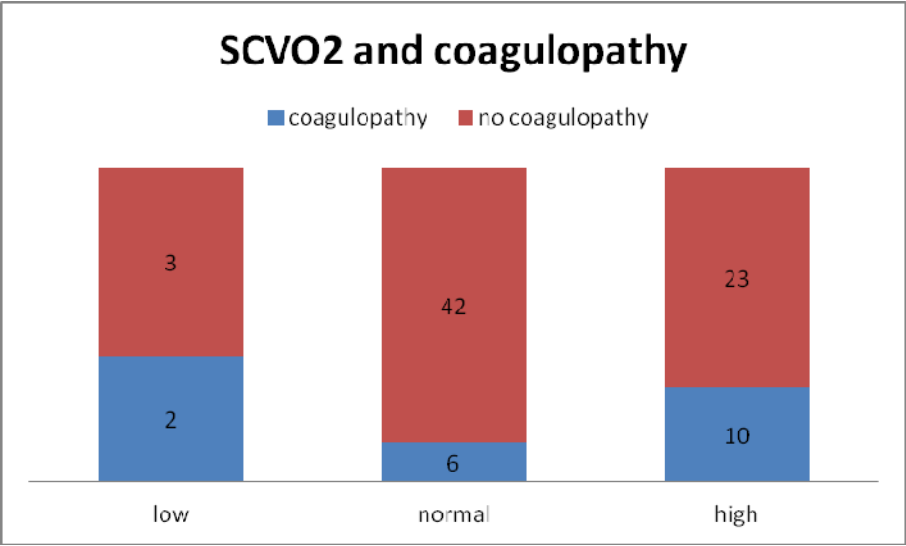
Apache II score as shown in earlier studies shows that it's a good indicator of mortality when the scores are high which is shown in figure 12.

When oxygen extraction ratio was compared, the hyperoxia group had significantly lower oxygen extraction ratio as shown in figure 13 below. But there when compared them both to mortality was no significance.

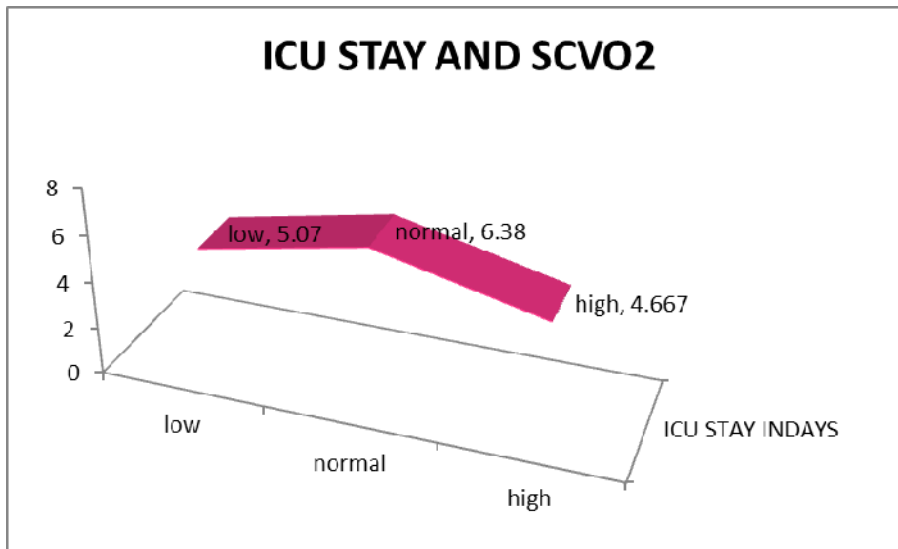


**Figure-13 Correlation of oxygen extraction ratio to ScvO2**

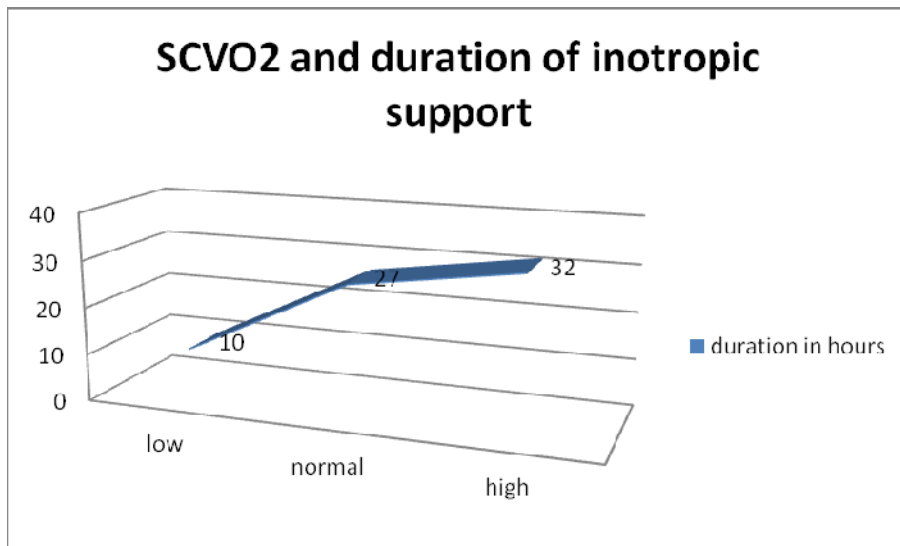
Next we saw the relation of SCVO2 with duration of ICU stay, need for dialysis, duration of inotropic supports and presence of coagulopathy which showed that both the hypoxia and the hyperoxia group required a slightly longer duration of inotropes ,more need for dialysis and presence of coagulopathy the data was not statistically significant .But when compared for the duration of ICU stay it was longer in the normoxia group probably as they had a better survival and the other groups had early mortality.



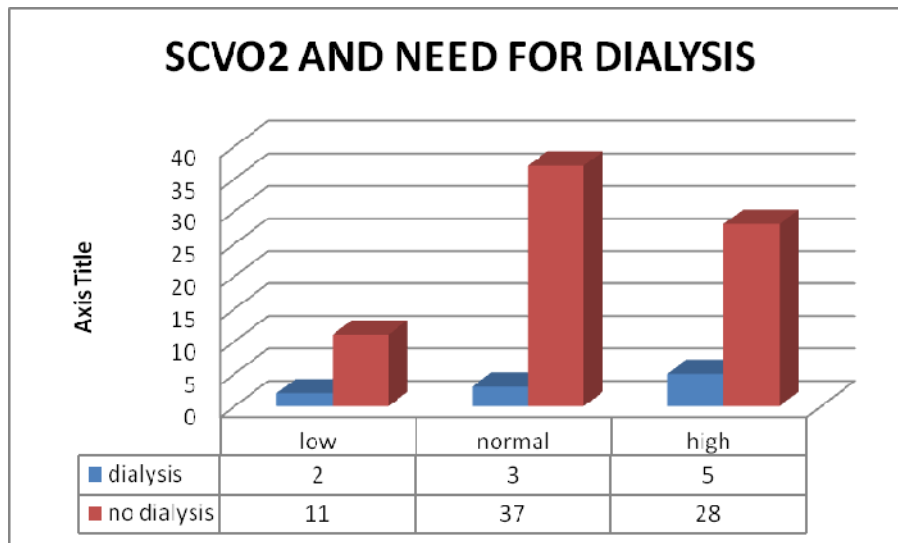
**Figure-14 incidence of coagulopathy with ScvO2**



**Figure-15 Duration of ICU stay and ScvO2**

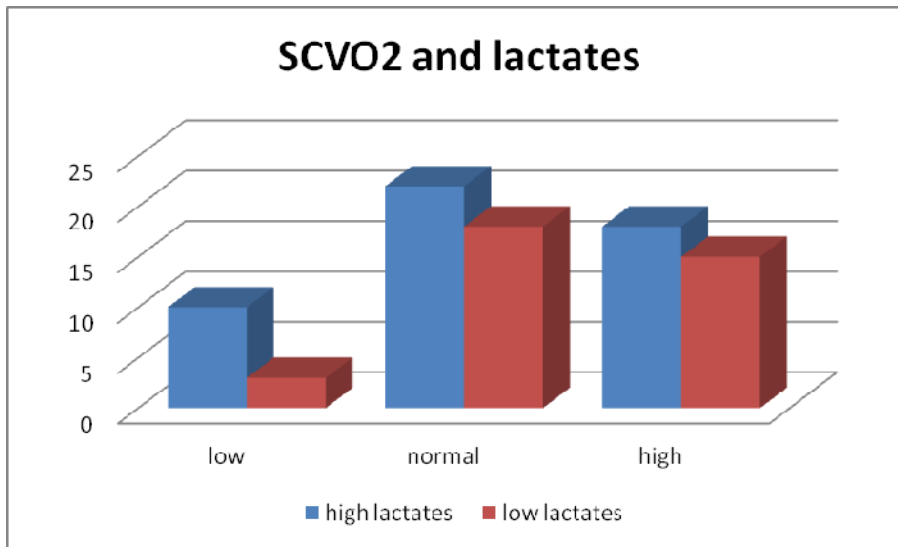


**Figure-16 Correlation of duration of inotropic support to ScvO2**

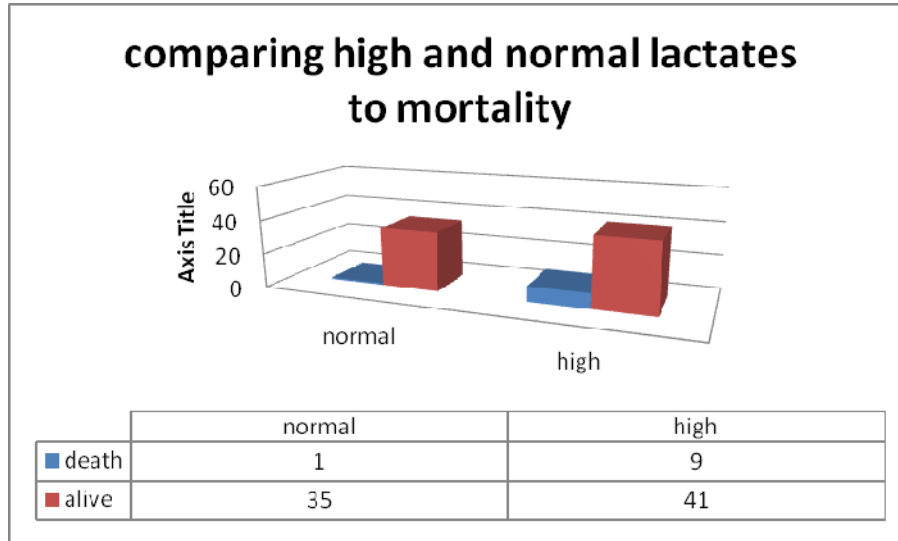


**Figure-17 ScvO2 and need for dialysis**

There was no statistically significant relation between the 3 groups of SCV02 when compared with APACHE II score, base excess, lactate levels. When lactates, base excess and Scv02 were compared to mortality though not significant gave a j shaped curve suggestive that mortality is higher both in the hypoxia and the hyperoxia group compared to the normoxia group.

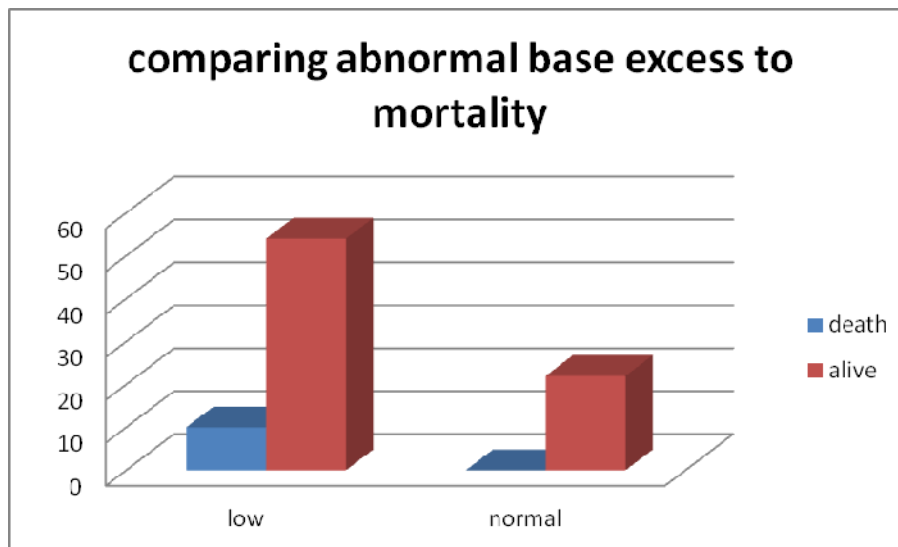


**Figure-18 ScvO2 and lactates**



**Figure-19 Correlation of lactate levels to mortality**





**Figure-20** Base excess to mortality

# DISCUSSION

A multicentre study by Pope et al in patients with diagnosis of sepsis showed that maximum SCVO<sub>2</sub> achieved in both hypoxia group and the hyperoxia group was associated with higher mortality and a multivariate analysis in the same study showed that hyperoxia was associated with increased mortality. Not many studies have been done which prove this association.(1)

In a large cohort of SICU patients we have found from multivariate modelling that in patients with hyperoxia (SCVO<sub>2</sub> >75%) at admission and 6 hours after admission have an increased risk of mortality compared to patients who had normoxia and hypoxia. These values highlight the potential significance of venous hyperoxia (or impaired oxygen utilisation) in sepsis and polytrauma patients. The probable reason for this is that while low SCVO<sub>2</sub> may be a marker for macrocirculatory failure, high SCVO<sub>2</sub> may reflect microcirculatory or mitochondrial failure. So further investigations to study the cause of impaired oxygen utilisation and possible interventions to improve this are necessary in these patients.

Tissue hypoperfusion can be present even in the presence of normal blood pressure and adequate cardiac output, a state sometimes called as cryptic shock. This may be maldistribution of blood flow at the microvascular level or related to mitochondrial dysfunction in the presence of adequate substrate delivery. The EGDT algorithm focusses on increasing systemic oxygen delivery or improving macrocirculation by increasing preload with intravenous volume expansion, increasing oxygen carrying capacity with packed red cells, increasing oxygen delivery with inotropes and increasing perfusion pressure with vasoconstrictors. But though the macrocirculatory failure is corrected, microcirculatory failure and mitochondrial failure potentially will result in dysoxia.(11)

In a study done by Mikkelsen(30) showed that initial high serum lactates was associated with mortality independent of clinically apparent shock in patients admitted to the emergency department with severe sepsis. Our data though not statistically significant shows higher mortality in higher lactate (>2mmols) group.

Our data also showed that patients with hyperoxia require a slightly longer duration of inotropes and higher need for dialysis with more coagulopathy but these were not statistically significant. Though mean duration of ICU stay was less in the hyperoxia group, this probably was because these patients died earlier. Also there was lower oxygen extraction ratio with higher mortality in hyperoxia group. This supports the concept of cellular hypoxia due to microcirculatory and mitochondrial failure despite adequate augmentation of macrocirculatory failure. The clinical relevance of mitochondrial dysfunction in septic shock was suggested by a study of 28 critically ill septic patients who underwent skeletal muscle biopsy within 24 hours of admission to the ICU. Skeletal muscle ATP concentrations, a marker of mitochondrial oxidative phosphorylation, were significantly lower in the 12 patients who died of sepsis than in 16 survivors. Thus, cell injury and death in sepsis may be explained by cytopathic (or histotoxic) anoxia, which is an inability to utilize delivered oxygen. The microcirculation (i.e., capillaries) may be the most important target in sepsis. Sepsis is associated with a decrease in the number of functional capillaries due to shunts. It is also associated with microthrombi and the blood flow is sluggish.(10)

At the level of the endothelium, sepsis induces phenotypic changes to endothelial cells. This occurs through direct and indirect interactions between the endothelial cells and components of the bacterial wall. In these situations, hyperlactemia indicates on-going tissue hypoperfusion due to misdistribution of flow in the microcirculation even after resuscitation and normalization of the macrocirculation. This shut-down of the vulnerable microcirculatory

units in the organ beds promotes the shunting of blood and hence oxygen, from arterial to venous compartment leaving the microcirculation hypoxic, along with a decrease in oxygen extraction. The local micro-circulatory partial pressure of oxygen drops below the venous oxygen pressure. This difference has been termed the "pO<sub>2</sub> gap" and is an indicator of the severity of functional shunting . The systemic manifestation of this pathologic shunting is seen as a deficit of oxygen extraction by tissues with an apparently normal delivery, and raised venous pO<sub>2</sub>, lactate, and gastric CO<sub>2</sub>, levels. Thus even with adequate macrocirculatory flow, the microcirculatory failure may prevent needed and available oxygen from reaching the cells in vital organs.(1)(31)

Hence we need further resuscitation protocol to assess microcirculatory failure and use therapies to improve microcirculation. We need to look at other markers of mitochondrial dysfunction as well as therapeutic approaches targeting these deficiencies. The finding that high scvo<sub>2</sub> was associated with increased mortality reminds us that dysoxia can occur despite adequate global oxygen delivery and that these abnormalities provide a target for further research.

This study is ongoing to complete the planned recruitment of 170 and the results may become statistically significant.

# CONCLUSIONS

This cohort study of sepsis and poly trauma patients admitted to Surgical ICU examined the relationship between scvo2 and the outcomes of ICU stay.

1. When compared to the normal group hyperoxia had a risk ratio 2.422 times more likely hood of mortality and the hypoxia group had 1.0256 times more likely hood of mortality .When the hypoxia group was compared with the hyperoxia group the risk ratio for mortality was 2.36 times more in the hyperoxia group though the p value was not significant .
2. When lactates, base excess and ScvO2 were compared to mortality though not significant gave a j shaped curve suggestive that mortality is higher both in the hypoxia and the hyperoxia group compared to the normoxia group.
3. When compared with oxygen extraction ratio those with hyperoxia had significantly lower oxygen extraction but no significant relation to icu mortality.
4. People with a mean apache 11 score of 22 had a significantly higher mortality, but in no relation to scvo2.

# **LIMITATIONS**

1. The small sample size though was adequate to predict a trend, was insufficient to address secondary objectives.
2. Few cases were initially resuscitated in the emergency department and later shifted to the intensive care unit which would have affected the initial Scvo2 values.
3. The number of cases of polytrauma were a meagre 12 % of the total sample size and therefore is difficult to comment on any particular trend.

# BIBLIOGRAPHY

1. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter Study of Central Venous Oxygen Saturation (ScvO<sub>2</sub>) as a Predictor of Mortality in Patients With Sepsis. *Annals of Emergency Medicine* 2010 Jan;55(1):40–46.e1.[cited 2012 Apr 4 ]
2. Perz S, Uhlig T, Kohl M, Bredle D, Reinhart K, Bauer M, Kortgen A. Low and “supranormal” central venous oxygen saturation and markers of tissue hypoxia in cardiac surgery patients: a prospective observational study. *Intensive Care Medicine* 2011 Jan;37(1):52–59.[cited 2012 Apr 4 ]
3. Should lactate clearance replace SvO<sub>2</sub> for sepsis EGD? (Pro/Con, CHEST)□» PulmCCM Central [Internet]. [date unknown];[cited 2012 Apr 6] Available from: <http://pulmccm.org/main/2012/critical-care-review/should-lactate-clearance-replace-scv2-in-egdt-procon-chest/>
4. cc3888.pdf [Internet]. [date unknown];[cited 2012 Apr 4] Available from: <http://www.biomedcentral.com/content/pdf/cc3888.pdf>
5. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality [Internet]. [date unknown];[cited 2012 Apr 6] Available from: [http://scienceindex.com/stories/1765954/High\\_central\\_venous\\_oxygen\\_saturation\\_in\\_the\\_latter\\_stages\\_of\\_septic\\_shock\\_is\\_associated\\_with\\_increased\\_mortality.html](http://scienceindex.com/stories/1765954/High_central_venous_oxygen_saturation_in_the_latter_stages_of_septic_shock_is_associated_with_increased_mortality.html)
6. High mixed venous oxygen saturation levels do not exclude fluid responsiveness in critically ill septic patients [Internet]. [date unknown];[cited 2012 Apr 6] Available from: [http://scienceindex.com/stories/1765953/High\\_mixed\\_venous\\_oxygen\\_saturation\\_levels\\_do\\_not\\_exclude\\_fluid\\_responsiveness\\_in\\_critically\\_ill\\_septic\\_patients.html](http://scienceindex.com/stories/1765953/High_mixed_venous_oxygen_saturation_levels_do_not_exclude_fluid_responsiveness_in_critically_ill_septic_patients.html)
7. Vincent J-L, Abraham E. The Last 100 Years of Sepsis. *Am. J. Respir. Crit. Care Med.* 2006 Feb;173(3):256–263.[cited 2012 Apr 8 ]
8. Pathophysiology of sepsis [Internet]. [date unknown];[cited 2012 Mar 19] Available from: <http://www.uptodate.com/contents/pathophysiology-of-sepsis>
9. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO<sub>2</sub>) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010 Jan;55(1):40–46.e1.[cited 2011 Feb 16 ]
10. Association between mitochondrial dysfunction and severity and outcome of septic shock□: The Lancet [Internet]. [date unknown];[cited 2012 Apr 4] Available from: [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(02\)09459-X/fulltext?refuid=S0196-0644\(09\)01440-1&refissn=0196-0644](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)09459-X/fulltext?refuid=S0196-0644(09)01440-1&refissn=0196-0644)

11. A T, Ak S, G G, M M. The Microcirculation in Sepsis. *Indian Journal of Anaesthesia* 2009 May;53(3):281.[cited 2012 Apr 9 ]
12. Reinhart K, Bloos F. The value of venous oximetry. *Curr Opin Crit Care* 2005 Jun;11(3):259–263.[cited 2012 Apr 4 ]
13. Fink MP. Bench-to-bedside review: Cytopathic hypoxia. *Crit Care* 2002 Dec;6(6):491–499.[cited 2012 Apr 8 ]
14. Rivers EP, Coba V, Visbal A, Whitmill M, Amponsah D. Management of sepsis: early resuscitation. *Clin. Chest Med.* 2008 Dec;29(4):689–704, ix–x.[cited 2012 Apr 6 ]
15. Management of severe sepsis and septic shock in adults [Internet]. [date unknown];[cited 2012 Apr 6] Available from: <http://www.uptodate.com/contents/management-of-severe-sepsis-and-septic-shock-in-adults>
16. Outcome Predictors in Patients With Severe Sepsis and Optimized Central Venous Oxygen Saturation - Full Text View - ClinicalTrials.gov [Internet]. [date unknown];[cited 2012 Apr 4] Available from: <http://clinicaltrials.gov/ct2/show/NCT01362829>
17. Maddirala S, Khan A. Optimizing Hemodynamic Support in Septic Shock Using Central and Mixed Venous Oxygen Saturation [Internet]. *Critical care clinics* [date unknown];26(2)[cited 2012 Apr 4] Available from: <http://cat.inist.fr/?aModele=afficheN&cpsidt=22736939>
18. Modification of oxygen extraction ratio by change in oxygen transport in septic shock. [Internet]. [date unknown];[cited 2012 Apr 8] Available from: <http://chestjournal.chestpubs.org/content/102/1/221.full.pdf+html>
19. *Annals of Emergency Medicine - Record* [Internet]. [date unknown];[cited 2012 Apr 4] Available from: [http://www.annemergmed.com/medline/record/ivp\\_03424642\\_31\\_1066](http://www.annemergmed.com/medline/record/ivp_03424642_31_1066)
20. Delaloye J, Baumgartner J-D, Calandra T. [Severe sepsis and septic shock]. *Rev Med Suisse* 2006 Apr;2(60):896–898, 900–902.[cited 2012 Apr 6 ]
21. Blasco V, Leone M, Textoris J, Visintini P, Albanèse J, Martin C. [Venous oximetry: physiology and therapeutic implications]. *Ann Fr Anesth Reanim* 2008 Jan;27(1):74–82.[cited 2012 Apr 4 ]
22. 077\_SV 2007 2(1) 6 - 10.pdf [Internet]. [date unknown];[cited 2012 Mar 18] Available from: [http://www.signavitae.com/attachments/077\\_SV%202007%202\(1\)%206%20-%2010.pdf](http://www.signavitae.com/attachments/077_SV%202007%202(1)%206%20-%2010.pdf)
23. Bakker J, Schievelde SJ, Brinkert W. [Serum lactate level as a indicator of tissue hypoxia in severely ill patients]. *Ned Tijdschr Geneesk* 2000 Apr;144(16):737–741.[cited 2012 Apr 4 ]
24. Azevedo L, Park M, Sanga R, Ferreira G, Palma L, Brauer L, Maciel A, Noritomi D, Ladeira J, Amaral A. Base excess and lactate as predictors of mortality in medical ICU patients. *Critical Care* 2004 Mar;8(Suppl 1):P328.[cited 2012 Apr 4 ]



25. cc10325.pdf [Internet]. [date unknown];[cited 2012 Apr 4] Available from:  
<http://ccforum.com/content/pdf/cc10325.pdf>
26. Di Filippo A, Gonnelli C, Perretta L, Zagli G, Spina R, Chiostrì M, Gensini GF, Peris A. Low central venous saturation predicts poor outcome in patients with brain injury after major trauma: a prospective observational study. *Scand J Trauma Resusc Emerg Med* 2009;17:23.[cited 2012 May 26 ]
27. doi:10.1016/j.injury.2004.12.037 [Internet]. [date unknown];[cited 2012 May 26] Available from:  
[https://docs.google.com/viewer?a=v&q=cache:Qke7RAf5SGIJ:www.akademiska.se/upload/48909/Keel%2520o%2520Trentz%2520Injury%25202005.pdf+Keel+M,+Trentz+O:+Pathophysiology+of+polytrauma.+Injury+2005,+36:691-709.&hl=en&gl=in&pid=bl&srcid=ADGEESg4A8t3QFpTjY\\_W7CZ-F1YXGN2AgUBYTQEaf-Zm3vINdGc4F2Ace4gzFRVT\\_3bMeNgBmYOBzZylXKfZWJUTmgovaleNZg5RCwD\\_BS4TFwxfv\\_o8qJjfnrQO3eKEfQJ8ycYS3I3H&sig=AHIEtbQeisdh6C1o2FPnPfVVRzO\\_XhrMCHA](https://docs.google.com/viewer?a=v&q=cache:Qke7RAf5SGIJ:www.akademiska.se/upload/48909/Keel%2520o%2520Trentz%2520Injury%25202005.pdf+Keel+M,+Trentz+O:+Pathophysiology+of+polytrauma.+Injury+2005,+36:691-709.&hl=en&gl=in&pid=bl&srcid=ADGEESg4A8t3QFpTjY_W7CZ-F1YXGN2AgUBYTQEaf-Zm3vINdGc4F2Ace4gzFRVT_3bMeNgBmYOBzZylXKfZWJUTmgovaleNZg5RCwD_BS4TFwxfv_o8qJjfnrQO3eKEfQJ8ycYS3I3H&sig=AHIEtbQeisdh6C1o2FPnPfVVRzO_XhrMCHA)
28. APACHEII.pdf [Internet]. [date unknown];[cited 2012 Apr 6] Available from:  
<http://www.healthcare.uiowa.edu/pharmacy/PTNews/2002/APACHEII.pdf>
29. Acute Physiology and Chronic Health Evaluation (APACHE II) Calculator [Internet]. [date unknown];[cited 2012 Apr 6] Available from:  
<http://clincalc.com/IcuMortality/APACHEII.aspx>
30. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, Bellamy SL, Christie JD. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit. Care Med.* 2009 May;37(5):1670–1677.[cited 2012 May 31 ]
31. Microcirculatory recruitment maneuvers co... [Minerva Anesthesiol. 2006] - PubMed - NCBI [Internet]. [date unknown];[cited 2012 Apr 8] Available from:  
<http://www.ncbi.nlm.nih.gov/pubmed/16682924>

# ANNEXURE

1. figure 1 Potential outcomes of mediator release in sepsis.
2. figure 2 Decreased oxygen extraction in sepsis.
3. figure 3 Oxygen transport.
4. figure 4 Early goal directed therapy(EGDT).
5. figure 5 Causes for deranged venous oxygen content(SvO<sub>2</sub>).
6. figure 6 Host defence response after trauma.
7. figure 7 Oxidative stress and capillary leakage.
8. figure 8 Distribution of SCVO<sub>2</sub> at admission.
9. figure 9 Distribution of SCVO<sub>2</sub> 6 hours after ICU admission.
10. figure 10 Correlation of ScvO<sub>2</sub> to mortality at admission.
11. figure 11 Correlation of ScvO<sub>2</sub> to mortality after 6 hours.
12. figure 12 Correlation of APACHE II score and mortality.
13. figure 13 Correlation of oxygen extraction ratio to ScvO<sub>2</sub>.
14. figure 14 incidence of coagulopathy with ScvO<sub>2</sub>.
15. figure 15 Duration of ICU stay and ScvO<sub>2</sub>.
16. figure 16 Correlation of duration of inotropic support to ScvO<sub>2</sub>.
17. figure 17 ScvO<sub>2</sub> and need for dialysis.
18. figure 18 ScvO<sub>2</sub> and lactates.
19. figure 19 Correlation of lactate levels to mortality.
20. figure 20 Base excess to mortality.
21. Table 1 Biologic effects of proinflammatory cytokines such as TNF and IL-1(8).
22. Table 2 Baseline data.

# STUDY TOOLS

## PATIENT INFORMATION SHEET

The department of Surgical Intensive care CMC Vellore is conducting a study to assess the impact of oxygen levels in the blood and blood lactate on the outcome in patients with diagnosis of sepsis and trauma.

If you/your relative agrees to participate in this study we will be collecting four blood samples (about 4 milliliters in total). The blood will be analysed and other information with regard to blood pressure and supportive care like ventilation will be recorded. There won't be any new changes in the treatment based on the results other than the standard changes we normally do. You / your relative will not have to pay extra anything for the tests or treatment. Your / your relative's condition will be assessed by the respective ICU team on a daily basis and the normal treatment will continue.

Your participation in the study is entirely voluntary and you are free to withdraw from the study at any point of time during the course of the study. Withdrawal from the study will not affect the treatment. The results from the blood tests and the other details related to heart, lungs and kidneys will be used for analysis. We will ensure that full confidentiality is maintained.

## INFORMED CONSENT

Study Title: A prospective observational study to characterize the association of abnormal central venous oxygen saturation to the morbidity and mortality in patients admitted to the Intensive Care unit with a diagnosis of sepsis or trauma.

Subject's Initials: \_\_\_\_\_ Subject's Name: \_\_\_\_\_

Date of Birth / Age: \_\_\_\_\_

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated \_\_\_\_\_ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signatory's Name: \_\_\_\_\_

Signature of the Investigator: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Study Investigator's Name: \_\_\_\_\_

Signature of the Witness: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Name of the Witness: \_\_\_\_\_

## DATA SHEET

Demographic data of patients coming to SICU with trauma or sepsis.

1. Age [years]
2. Sex [no. of patients] female/male
3. Body mass index [kg m<sup>-2</sup>]
4. Co morbidities
5. Chronic medication
6. APACHE II Score 24 hours after admission
7. Hemoglobin level  
At admission  
After 6 hours
8. Transfusion requirements
9. Central venous oxygen saturation  
At admission  
After 6 hours
10. Lactate [mmol/l]  
At admission  
After 6 hours

11. Base excess

At admission

After 6 hours

12. Vital parameters

a. Heart rate

At admission

After 6 hours

b. Blood pressure

At admission

After 6 hours

c. Respiratory rate

At admission

After 6 hours

d. Oxygen saturation

At admission

After 6 hours

13. Duration of icu stay

14. Duration of ventilation

15. Duration of inotropic support

16. Need for dialysis

17. ICU mortality

18. 28 day hospital mortality



